



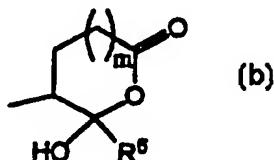
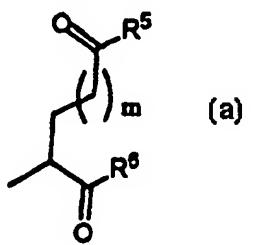
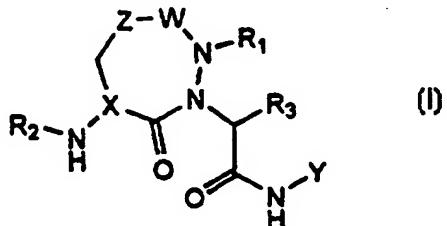
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(71) Applicant ( <i>for all designated States except US</i> ): VERTEX PHARMACEUTICALS INCORPORATED [US/US]; 130 Waverly Street, Cambridge, MA 02139-4242 (US).			
(72) Inventors; and			
(75) Inventors/Applicants ( <i>for US only</i> ): WANNAMAKER, Marion, W. [US/US]; 375 Harvard Road, Stow, MA 01775 (US). CHARIFSON, Paul [US/US]; 7 Dartmouth Drive, Framingham, MA 01701 (US). LAUFFER, David, J. [US/US]; 254 Taylor Road, Stow, MA 01775 (US). MULLICAN, Michael, D. [US/US]; 110 Parker Road, Needham, MA 02194 (US).			
(74) Agents: HALEY, James, F., Jr.; Fish & Neave, 1251 Avenue of the Americas, New York, NY 10020 (US) et al.			
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(54) Title: 1,2-DIAZEPANE DERIVATIVES AS INTERLEUKIN-1BETA CONVERTING ENZYME INHIBITORS

(57) Abstract

The present invention relates to novel classes of compounds which are caspase inhibitors, in particular interleukin-1 $\beta$  converting enzyme ("ICE") inhibitors represented by formula (I), wherein Y is (a) or (b). This invention also relates to methods for inhibiting caspase activity and decreasing IGIF production and IFN- $\gamma$  production and methods for treating interleukin-1, apoptosis-, and interferon- $\gamma$ -mediated diseases using the compounds and compositions of this invention. This invention also relates to methods of preparing the compounds of this invention.



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## 5 1,2-DIAZEPANE DERIVATIVES AS INTERLEUKIN-1BETA CONVERTING ENZYME INHIBITORS

TECHNICAL FIELD OF THE INVENTION

The present invention relates to novel classes of compounds which are caspase inhibitors, in particular interleukin-1 $\beta$  converting enzyme ("ICE") inhibitors.

This invention also relates to pharmaceutical compositions comprising these compounds. The compounds and pharmaceutical compositions of this invention are particularly well suited for inhibiting caspase activity and consequently, may be advantageously used as agents against interleukin-1- ("IL-1"), apoptosis-, interferon- $\gamma$  inducing factor- (IGIF), or interferon- $\gamma$ - ("IFN- $\gamma$ ") mediated diseases, including inflammatory diseases; autoimmune diseases, destructive bone disorders, proliferative disorders, infectious diseases, and degenerative diseases. This invention also relates to methods for inhibiting caspase activity and decreasing IGIF production and IFN- $\gamma$  production and methods for treating interleukin-1, apoptosis-, and interferon- $\gamma$ - mediated diseases using the compounds and compositions of this invention. This invention also relates to methods of preparing the compounds of this invention.

BACKGROUND OF THE INVENTION

Interleukin 1 ("IL-1") is a major pro-inflammatory and immunoregulatory protein that stimulates fibroblast differentiation and proliferation, the production of prostaglandins, collagenase and phospholipase by synovial cells and chondrocytes,

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basophil and eosinophil degranulation and neutrophil activation. Oppenheim, J.H. et al, Immunology Today, 7, pp. 45-56 (1986). As such, it is involved in the pathogenesis of chronic and acute inflammatory and 5 autoimmune diseases. For example, in rheumatoid arthritis, IL-1 is both a mediator of inflammatory symptoms and of the destruction of the cartilage proteoglycan in afflicted joints. Wood, D.D. et al., Arthritis Rheum. 26, 975, (1983); Pettipher, E.J. et al., 10 Proc. Natl. Acad. Sci. USA 71, 295 (1986); Arend, W.P. and Dayer, J.M., Arthritis Rheum. 38, 151 (1995). IL-1 is also a highly potent bone resorption agent. Jandiski, J.J., J. Oral Path. 17, 145 (1988); Dewhirst, F.E. et al., J. Immunol. 8, 2562 1985). It is alternately referred to 15 as "osteoclast activating factor" in destructive bone diseases such as osteoarthritis and multiple myeloma. Bataille, R. et al., Int. J. Clin. Lab. Res. 21(4), 283 (1992). In certain proliferative disorders, such as acute myelogenous leukemia and multiple myeloma, IL-1 can 20 promote tumor cell growth and adhesion. Bani, M.R., J. Natl. Cancer Inst. 83, 123 (1991); Vidal-Vanaclocha, F., Cancer Res. 54, 2667 (1994). In these disorders, IL-1 also stimulates production of other cytokines such as IL-6, which can modulate tumor development (Tartour et al., 25 Cancer Res. 54, p. 6243 (1994)). IL-1 is predominantly produced by peripheral blood monocytes as part of the inflammatory response and exists in two distinct agonist forms, IL-1 $\alpha$  and IL-1 $\beta$ . Mosely, B.S. et al., Proc. Natl. Acad. Sci., 84, pp. 4572-4576 (1987); Lonnemann, G. et 30 al., Eur. J. Immunol., 19, pp. 1531-1536 (1989).

IL-1 $\beta$  is synthesized as a biologically inactive precursor, pIL-1 $\beta$ . pIL-1 $\beta$  lacks a conventional leader sequence and is not processed by a signal peptidase. March, C.J., Nature, 315, pp. 641-647 (1985). Instead, 35 pIL-1 $\beta$  is cleaved by interleukin-1 $\beta$  converting enzyme

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("ICE") between Asp-116 and Ala-117 to produce the biologically active C-terminal fragment found in human serum and synovial fluid. Sleath, P.R., et al., J. Biol. Chem., 265, pp. 14526-14528 (1992); A.D. Howard et al., 5 J. Immunol., 147, pp. 2964-2969 (1991). ICE is a cysteine protease localized primarily in monocytes. It converts precursor IL-1 $\beta$  to the mature form. Black, R.A. et al., FEBS Lett., 247, pp. 386-390 (1989); Kostura, M.J. et al., Proc. Natl. Acad. Sci. U.S.A., 86, pp. 5227-10 5231 (1989). Processing by ICE is also necessary for the transport of mature IL-1 $\beta$  through the cell membrane.

ICE is a member of a family of homologous enzymes called caspases. These homologs have sequence similarities in the active site regions of the enzymes. 15 Such homologs (caspases) include TX (or ICE<sub>rel-II</sub> or ICH-2) (Faucheu, et al., EMBO J., 14, p. 1914 (1995); Kamens J., et al., J. Biol. Chem., 270, p. 15250 (1995); Nicholson et al., J. Biol. Chem., 270 15870 (1995)), TY (or ICE<sub>rel-III</sub>) (Nicholson et al., J. Biol. Chem., 270, 20 p. 15870 (1995); ICH-1 (or Nedd-2) (Wang, L. et al., Cell, 78, p. 739 (1994)), MCH-2, (Fernandes-Alnemri, T. et al., Cancer Res., 55, p. 2737 (1995), CPP32 (or YAMA or apopain) (Fernandes-Alnemri, T. et al., J. Biol. Chem., 269, p. 30761 (1994); Nicholson, D.W. et al., 25 Nature, 376, p. 37 (1995)), and CMH-1 (or MCH-3) (Lippke, et al., J. Biol. Chem., (1996); Fernandes-Alnemri, T. et al., Cancer Res., (1995)).

Each of these ICE homologs, as well as ICE itself, is capable of inducing apoptosis when 30 overexpressed in transfected cell lines. Inhibition of one or more of these homologs with the peptidyl ICE inhibitor Tyr-Val-Ala-Asp-chloromethylketone results in inhibition of apoptosis in primary cells or cell lines. Lazebnik et al., Nature, 371, p. 346 (1994).

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Caspases also appear to be involved in the regulation of programmed cell death or apoptosis. Yuan, J. et al., Cell, 75, pp. 641-652 (1993); Miura, M. et al., Cell, 75, pp. 653-660 (1993); Nett-Fiordalisi, M.A. et al., J. Cell Biochem., 17B, p. 117 (1993). In particular, ICE or ICE homologs are thought to be associated with the regulation of apoptosis in neurodegenerative diseases, such as Alzheimer's and Parkinson's disease. Marx, J. and M. Baringa, Science, 259, pp. 760-762 (1993); Gagliardini, V. et al., Science, 263, pp. 826-828 (1994). Therapeutic applications for inhibition of apoptosis may include treatment of Alzheimer's disease, Parkinson's disease, stroke, myocardial infarction, spinal atrophy, and aging.

ICE has been demonstrated to mediate apoptosis (programmed cell death) in certain tissue types. Steller, H., Science, 267, p. 1445 (1995); Whyte, M. and Evan, G., Nature, 376, p. 17 (1995); Martin, S.J. and Green, D.R., Cell, 82, p. 349 (1995); Alnemri, E.S., et al., J. Biol. Chem., 270, p. 4312 (1995); Yuan, J. Curr. Opin. Cell Biol., 7, p. 211 (1995). A transgenic mouse with a disruption of the ICE gene is deficient in Fas-mediated apoptosis (Kuida, K. et al., Science 267, 2000 (1995)). This activity of ICE is distinct from its role as the processing enzyme for pro-IL-1 $\beta$ . It is conceivable that in certain tissue types, inhibition of ICE may not affect secretion of mature IL-1 $\beta$ , but may inhibit apoptosis.

Enzymatically active ICE has been previously described as a heterodimer composed of two subunits, p20 and p10 (20kDa and 10kDa molecular weight, respectively). These subunits are derived from a 45kDa proenzyme (p45) by way of a p30 form, through an activation mechanism that is autocatalytic. Thornberry, N.A. et al., Nature, 356, pp. 768-774 (1992). The ICE proenzyme has been

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divided into several functional domains: a prodomain (p14), a p22/20 subunit, a polypeptide linker and a p10 subunit. Thornberry et al., supra; Casano et al., Genomics, 20, pp. 474-481 (1994).

5 Full length p45 has been characterized by its cDNA and amino acid sequences. PCT patent applications WO 91/15577 and WO 94/00154. The p20 and p10 cDNA and amino acid sequences are also known. Thornberry et al., supra. Murine and rat ICE have also been sequenced and  
10 cloned. They have high amino acid and nucleic acid sequence homology to human ICE. Miller, D.K. et al., Ann. N.Y. Acad. Sci., 696, pp. 133-148 (1993); Molineaux, S.M. et al., Proc. Nat. Acad. Sci., 90, pp. 1809-1813 (1993). The three-dimensional structure of ICE has been  
15 determined at atomic resolution by X-ray crystallography. Wilson, K.P., et al., Nature, 370, pp. 270-275 (1994). The active enzyme exists as a tetramer of two p20 and two p10 subunits.

Recently, ICE and other members of the ICE/CED-  
20 3 family have been linked to the conversion of pro-IGIF to IGIF or to the production of IFN- $\gamma$  in vivo (PCT application PCT/US96/20843, filed 12/20/96, published 6/26/97 under publication no. WO 97/22619, which is incorporated herein by reference). IGIF is synthesized  
25 in vivo as the precursor protein "pro-IGIF".

Interferon-gamma inducing factor (IGIF) is an approximately 18-kDa polypeptide that stimulates T-cell production of interferon-gamma (IFN- $\gamma$ ). IGIF is produced by activated Kupffer cells and macrophages in vivo and is  
30 exported out of such cells upon endotoxin stimulation. Thus, a compound that decreases IGIF production would be useful as an inhibitor of such T-cell stimulation which in turn would reduce the levels of IFN- $\gamma$  production by those cells.

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IFN- $\gamma$  is a cytokine with immunomodulatory effects on a variety of immune cells. In particular, IFN- $\gamma$  is involved in macrophage activation and Th1 cell selection (F. Belardelli, APMIS, 103, p. 161 (1995)).

5 IFN- $\gamma$  exerts its effects in part by modulating the expression of genes through the STAT and IRF pathways (C. Schindler and J.E. Darnell, Ann. Rev. Biochem., 64, p. 621 (1995); T. Taniguchi, J. Cancer Res. Clin. Oncol., 121, p. 516 (1995)).

10 Mice lacking IFN- $\gamma$  or its receptor have multiple defects in immune cell function and are resistant to endotoxic shock (S. Huang et al., Science, 259, p. 1742 (1993); D. Dalton et al., Science, 259, p. 1739 (1993); B.D. Car et al., J. Exp. Med., 179, p. 1437 (1994)).

15 Along with IL-12, IGIF appears to be a potent inducer of IFN- $\gamma$  production by T cells (H. Okamura et al., Infection and Immunity, 63, p. 3966 (1995); H. Okamura et al., Nature, 378, p. 88 (1995); S. Ushio et al., J. Immunol., 156, p. 4274 (1996)).

20 IFN- $\gamma$  has been shown to contribute to the pathology associated with a variety of inflammatory, infectious and autoimmune disorders and diseases. Thus, compounds capable of decreasing IFN- $\gamma$  production would be useful to ameliorate the effects of IFN- $\gamma$  related pathologies.

25 Accordingly, compositions and methods capable of regulating the conversion of pro-IGIF to IGIF would be useful for decreasing IGIF and IFN- $\gamma$  production in vivo, and thus for ameliorating the detrimental effects of these proteins which contribute to human disorders and diseases.

30 Caspase inhibitors represent a class of compounds useful for the control of inflammation or apoptosis or both. Peptide and peptidyl inhibitors of ICE have been described. PCT patent applications WO  
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91/15577; WO 93/05071; WO 93/09135; WO 93/14777 and WO 93/16710; and European patent application 0 547 699. Such peptidyl inhibitors of ICE have been observed to block the production of mature IL-1 $\beta$  in a mouse model of 5 inflammation (vide infra) and to suppress growth of leukemia cells in vitro (Estrov et al., Blood 84, 380a (1994)). However, due to their peptidic nature, such inhibitors are typically characterized by undesirable pharmacologic properties, such as poor cellular 10 penetration and cellular activity, poor oral absorption, poor stability and rapid metabolism. Plattner, J.J. and D.W. Norbeck, in Drug Discovery Technologies, C.R. Clark and W.H. Moos, Eds. (Ellis Horwood, Chichester, England, 1990), pp. 92-126. This has hampered their development 15 into effective drugs.

Non-peptidyl compounds have also been reported to inhibit ICE in vitro. PCT patent application WO 95/26958; US Patent 5,552,400; Dolle et al., J. Med. Chem., 39, pp. 2438-2440 (1996). It is not clear however 20 whether these compounds have the appropriate pharmacological profiles to be therapeutically useful.

Accordingly, the need exists for compounds that can effectively inhibit caspases for use as agents for preventing and treating chronic and acute forms of IL-1-mediated diseases, apoptosis-, IGF-, or IFN- $\gamma$ -mediated 25 diseases, as well as inflammatory, autoimmune, destructive bone, proliferative, infectious, or degenerative diseases.

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#### SUMMARY OF THE INVENTION

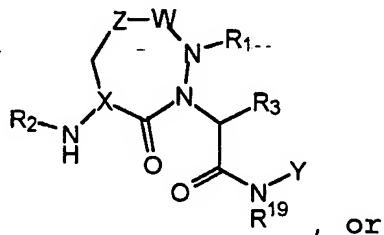
The present invention provides novel classes of compounds, and pharmaceutically acceptable derivatives thereof, that are useful as caspases inhibitors, in particular as ICE inhibitors. These compounds can be 35 used alone or in combination with other therapeutic or

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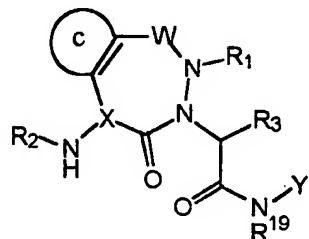
prophylactic agents, such as antibiotics, immunomodulators or other anti-inflammatory agents, for the treatment or prophylaxis of diseases mediated by IL-1, apoptosis, IGIF or IFN- $\gamma$ . According to a preferred 5 embodiment, the compounds of this invention are capable of binding to the active site of ICE and inhibiting the activity of that enzyme.

It is a principal object of this invention to provide novel classes of compounds represented by 10 formulas:

(I)



(II)



wherein the various substituents are described 15 herein.

This invention also provides compositions comprising compounds represented by formulae (I) and (II), methods for using these compositions in the treatment or prevention of various disorders, and methods 20 for preparing these compounds.

DETAILED DESCRIPTION OF THE INVENTION

In order that the invention described herein may be more fully understood, the following detailed description is set forth.

5       The following abbreviations and definitions are used throughout the application.

Abbreviations

	Ac <sub>2</sub> O	acetic anhydride
	n-Bu	normal-butyl
10	DMF	dimethylformamide
	DIEA	N,N-diisopropylethylamine
	EDC	1-(3-Dimethylaminopropyl)-3- ethylcarbodiimide hydrochloride
	Et <sub>2</sub> O	diethyl ether
15	EtoAc	ethyl acetate
	Fmoc	9-fluorenylmethyloxycarbonyl
	HBTU	O-benzotriazol-1-yl-N,N,N',N'- tetramethyluronium hexafluorophosphate
	HOBT	1-hydroxybenzotriazole hydrate
20	MeOH	methanol
	TFA	trifluoroacetic acid

The term "caspase" refers to an enzyme that is a member of the family of enzymes that includes ICE (see 25 H. Hara, Natl. Acad. Sci., 94, pp. 2007-2012 (1997).

The terms "HBV", "HCV" and "HGV" refer to hepatitis-B virus, hepatitis-C virus and hepatitis-G virus, respectively.

The term "K<sub>i</sub>" refers to a numerical measure of 30 the effectiveness of a compound in inhibiting the activity of a target enzyme such as ICE. Lower values of K<sub>i</sub> reflect higher effectiveness. The K<sub>i</sub> value is a derived by fitting experimentally determined rate data to standard enzyme kinetic equations (see I.H. Segel, Enzyme Kinetics, Wiley-Interscience, 1975).

The term "interferon gamma inducing factor" or "IGIF" refers to a factor which is capable of stimulating the endogenous production of IFN- $\gamma$ .

The term "caspase inhibitor" refers to a compound which is capable of demonstrating detectable inhibition of one or more caspases. The term "ICE inhibitor" refers to a compound which is capable of demonstrating detectable inhibition of ICE and optionally of one or more additional caspases. Inhibition of these enzymes may be determined using the methods described and incorporated by reference herein. The skilled practitioner realizes that an in vivo enzyme inhibitor is not necessarily an in vitro enzyme inhibitor. For example, a prodrug form of a compound typically demonstrates little or no activity in in vitro assays. Such prodrug forms may be altered by metabolic or other biochemical processes in the patient to provide an in vivo enzyme inhibitor.

The term "cytokine" refers to a molecule which mediates interactions between cells.

The term "condition" refers to any disease, disorder or effect that produces deleterious biological consequences in a subject.

The term "subject" refers to an animal, or to one or more cells derived from an animal. Preferably, the animal is a mammal, most preferably a human. Cells may be in any form, including but not limited to cells retained in tissue, cell clusters, immortalized cells, transfected or transformed cells, and cells derived from an animal that have been physically or phenotypically altered.

The term "patient" as used in this application refers to any mammal, preferably humans.

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The term "alkyl" refers to a straight-chained or branched, saturated aliphatic hydrocarbon containing 1 to 6 carbon atoms.

5 The term "alkenyl" refers to a straight-chained or branched unsaturated hydrocarbon containing 2 to 6 carbon atoms and at least one double bond.

The term "alkynyl" refers to a straight-chained or branched unsaturated hydrocarbon containing 2 to 6 carbon atoms and at least one triple bond.

10 The term "cycloalkyl" refers to a mono- or polycyclic, non-aromatic, hydrocarbon ring system which may optionally contain unsaturated bonds in the ring system. Examples include cyclohexyl, adamantyl and norbornyl.

15 The term "aryl" refers to a mono- or polycyclic ring system which contains 6, 10, 12 or 14 carbons in which at least one ring of the ring system is aromatic. The aryl groups of this invention are optionally singly or multiply substituted with R<sup>17</sup>. Examples of aryl ring systems include, phenyl, naphthyl, and 20 tetrahydronaphthyl.

25 The term "heteroaryl" refers to a mono- or polycyclic ring system which contains 1 to 15 carbon atoms and 1 to 4 heteroatoms, and in which at least one ring of the ring system is aromatic. Heteroatoms are sulfur, nitrogen or oxygen. The heteroaryl groups of this invention are optionally singly or multiply substituted with R<sup>17</sup>.

30 The term "heterocyclic" refers to a mono- or polycyclic ring system which contains 1 to 15 carbon atoms and 1 to 4 heteroatoms, in which the mono- or polycyclic ring system may optionally contain unsaturated bonds but is not aromatic. Heteroatoms are independently sulfur, nitrogen, or oxygen.

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The term "alkylaryl" refers to an alkyl group, wherein one or more hydrogen atoms of the alkyl group is replaced by one or more aryl radical.

5 The term "alkylheteroaryl" refers to an alkyl group, wherein a hydrogen atom of the alkyl group is replaced by a heteroaryl radical.

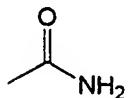
The term "substitute" refers to the replacement of a hydrogen atom in a compound with a substituent group.

10 The term "straight chain" refers to a contiguous unbranching string of covalently bound atoms.

The straight chain may be substituted, but these substituents are not a part of the straight chain.

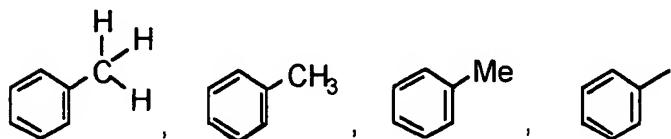
15 The term "amino acid side chain" refers to the substituent bound to the  $\alpha$ -carbon of either a natural or a non-natural  $\alpha$ -amino acid.

20 In chemical formulas, parenthesis are used herein to denote connectivity in molecules or groups. In particular, parentheses are used to indicate: 1) that more than one atom or group is bonded to a particular atom; or 2) a branching point (i.e., the atom immediately before the open parenthesis is bonded both to the atom or group in the parentheses and the atom or group immediately after the closed parenthesis). An example of 25 the first use is "-N(alkyl)<sub>2</sub>", indicating two alkyl groups bond to an N atom. An example of the second use is "-C(O)NH<sub>2</sub>", indicating a carbonyl group and an amino ("NH<sub>2</sub>") group both bonded to the indicated carbon atom. A "-C(O)NH<sub>2</sub>" group may be represented in other ways, 30 including the following structure:



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Substituents may be represented in various forms. These various forms are known to the skilled practitioner and may be used interchangeably. For example, a methyl substituent on a phenyl ring may be 5 represented in any of the following forms:

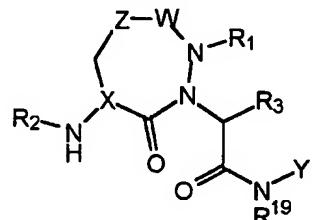


Various forms of substituents such as methyl are used herein interchangeably.

10 Other definitions are set forth in the specification where necessary.

#### Compounds of this Invention

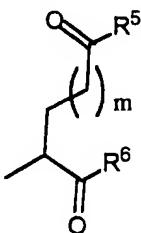
15 The compounds of one embodiment (A) of this invention are those of formula (I):



wherein:

Y is:

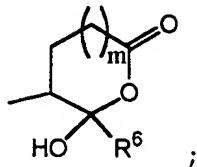
20 (a)



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provided that when R<sup>5</sup> is -OH then Y can also be:

(b)



5           m is 0 or 1;

W is -CH<sub>2</sub>- , -C(O)- , S(O)<sub>2</sub> , or -S(O)- ;

10           X is -C(H)- , -C(R<sup>8</sup>)- , or -N- ;

Z is -CH<sub>2</sub>- , -O- , -S- , or -N(R<sup>1</sup>)- , provided that if Z is -N(R<sup>1</sup>)- , then W is -C(O)- , -S(O)<sub>2</sub>- , or -S(O)- ;

15           each R<sup>1</sup> is independently -H , -C(O)R<sup>8</sup> , -S(O)<sub>2</sub>R<sup>8</sup> , -S(O)R<sup>8</sup> , -R<sup>21</sup> , -alkyl-R<sup>21</sup> , -alkenyl-R<sup>21</sup> , or -alkynyl-R<sup>21</sup> ;

20           R<sup>2</sup> is -C(O)R<sup>8</sup> , -C(O)C(O)R<sup>8</sup> , -S(O)<sub>2</sub>R<sup>8</sup> , -S(O)R<sup>8</sup> , -C(O)OR<sup>8</sup> , -C(O)N(H)R<sup>8</sup> , -S(O)<sub>2</sub>N(H)-R<sup>8</sup> , -S(O)N(H)-R<sup>8</sup> , -C(O)C(O)N(H)R<sup>8</sup> , -C(O)CH=CHR<sup>8</sup> , -C(O)CH<sub>2</sub>OR<sup>8</sup> , -C(O)CH<sub>2</sub>N(H)R<sup>8</sup> , -C(O)N(R<sup>8</sup>)<sub>2</sub> , -S(O)<sub>2</sub>N(R<sup>8</sup>)<sub>2</sub> , -S(O)N(R<sup>8</sup>)<sub>2</sub> , -C(O)C(O)N(R<sup>8</sup>)<sub>2</sub> , -C(O)CH<sub>2</sub>N(R<sup>8</sup>)<sub>2</sub> , -CH<sub>2</sub>-R<sup>8</sup> , -CH<sub>2</sub>-alkenyl-R<sup>8</sup> , or -CH<sub>2</sub>-alkynyl-R<sup>8</sup> ;

25           R<sup>3</sup> is -H , -R<sup>21</sup> , -alkyl-R<sup>21</sup> , -alkenyl-R<sup>21</sup> , or -alkynyl-R<sup>21</sup> ;

30           each R<sup>4</sup> is independently -OH , -F , -Cl , -Br , -I , -NO<sub>2</sub> , -CN , -NH<sub>2</sub> , -CO<sub>2</sub>H , -C(O)NH<sub>2</sub> , -N(H)C(O)H , -N(H)C(O)NH<sub>2</sub> , -alkyl , -cycloalkyl , -perfluoroalkyl , -O-alkyl , -N(H)alkyl , -N(alkyl)<sub>2</sub> , -C(O)N(H)alkyl ,

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-C(O)N(alkyl)<sub>2</sub>, -N(H)C(O)alkyl, -N(H)C(O)N(H)alkyl,  
 -N(H)C(O)N(alkyl)<sub>2</sub>, -S-alkyl, -S(O)<sub>2</sub>alkyl, -S(O)alkyl,  
 -C(O)alkyl, -CH<sub>2</sub>NH<sub>2</sub>, -CH<sub>2</sub>N(H)alkyl, -CH<sub>2</sub>N(alkyl)<sub>2</sub>, or  
 -N(H)C(O)Oalkyl;

5

R<sup>5</sup> is -OH, -OR<sup>8</sup>, or -N(H)OH;

R<sup>6</sup> is -H, -CH<sub>2</sub>OR<sup>9</sup>, -CH<sub>2</sub>SR<sup>10</sup>, -CH<sub>2</sub>N(H)R<sup>9</sup>,  
 -CH<sub>2</sub>N(R<sup>9</sup>)R<sup>11</sup>, -C(H)N<sub>2</sub>, -CH<sub>2</sub>F, -CH<sub>2</sub>Cl, -C(O)N(R<sup>11</sup>)<sub>2</sub>, -R<sup>13</sup>,  
 10 or -R<sup>14</sup>;

15

each R<sup>8</sup> is independently -alkyl, -cycloalkyl,  
 -aryl, -heteroaryl, -heterocyclyl, -alkylcycloalkyl  
 -alkylaryl, -alkylheteroaryl, or -alkylheterocyclyl;

15

R<sup>9</sup> is -H, -C(O)aryl, -C(O)heteroaryl,  
 -C(O)alkylaryl, -C(O)alkylheteroaryl, -alkylaryl,  
 -alkylheteroaryl, -aryl, -heteroaryl, or -P(O)(R<sup>15</sup>)<sub>2</sub>;

20

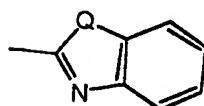
R<sup>10</sup> is -alkylaryl or -alkylheteroaryl;

each R<sup>11</sup> is independently -H, -alkyl, -aryl,  
 -heteroaryl, -cycloalkyl, -alkylaryl, or  
 -alkylheteroaryl;

25

R<sup>13</sup> is -alkylaryl or -alkylheteroaryl;

R<sup>14</sup> is



(i)



(ii)



(iii)



(iv)

30

wherein Q is -O- or -S-, any hydrogen atom in (i) is optionally replaced with -R<sup>17</sup>, and any hydrogen atom in (ii), (iii), and (iv) is optionally replaced with -R<sup>17</sup>, -R<sup>18</sup> or -alkyl-R<sup>18</sup>;

- each R<sup>15</sup> is independently -H, -OH, -alkyl,  
-aryl, -heteroaryl, -cycloalkyl, -alkylaryl,  
-alkylheteroaryl, -Oalkyl, -Oaryl, -Oheteroaryl,  
5 -Oalkylaryl, or -Oalkylheteroaryl;
- each R<sup>17</sup> is independently -OH, -F, -Cl, -Br,  
-I, -NO<sub>2</sub>, -CN, -NH<sub>2</sub>, -CO<sub>2</sub>H, -C(O)NH<sub>2</sub>, -N(H)C(O)H,  
-N(H)C(O)NH<sub>2</sub>, -SO<sub>2</sub>NH<sub>2</sub>, -C(O)H, -alkyl, -cycloalkyl,  
10 -perfluoroalkyl, -O-alkyl, -N(H)alkyl, -N(alkyl)<sub>2</sub>,  
-CO<sub>2</sub>alkyl, -C(O)N(H)alkyl, -C(O)N(alkyl)<sub>2</sub>,  
-N(H)C(O)alkyl, -N(H)C(O)N(H)alkyl, -N(H)C(O)N(alkyl)<sub>2</sub>,  
-S(O)<sub>2</sub>N(H)alkyl, -S(O)N(H)alkyl, -S(O)<sub>2</sub>N(alkyl)<sub>2</sub>,  
-S(O)N(alkyl)<sub>2</sub>, -S-alkyl, -S(O)<sub>2</sub>alkyl, -S(O)alkyl, or  
15 -C(O)alkyl;
- each R<sup>18</sup> is independently -aryl, -heteroaryl,  
-alkylaryl, -alkylheteroaryl, -O-aryl, -O-heteroaryl,  
-O-alkylaryl, -O-alkylheteroaryl, -N(H)aryl, -N(aryl)<sub>2</sub>,  
20 -N(H)heteroaryl, -N(heteroaryl)<sub>2</sub>, -N(H)alkylaryl,  
-N(alkylaryl)<sub>2</sub>, -N(H)alkylheteroaryl,  
-N(alkylheteroaryl)<sub>2</sub>, -S-aryl, -S-heteroaryl,  
-S-alkylaryl, -S-alkylheteroaryl, -C(O)aryl,  
-C(O)heteroaryl, -C(O)alkylaryl, -C(O)alkylheteroaryl,  
25 -CO<sub>2</sub>aryl, -CO<sub>2</sub>heteroaryl, -CO<sub>2</sub>alkylaryl,  
-CO<sub>2</sub>alkylheteroaryl, -C(O)N(H)aryl, -C(O)N(aryl)<sub>2</sub>,  
-C(O)N(H)heteroaryl, -C(O)N(heteroaryl)<sub>2</sub>,  
-C(O)N(H)alkylaryl, -C(O)N(alkylaryl)<sub>2</sub>,  
-C(O)N(H)alkylheteroaryl, -C(O)N(alkylheteroaryl)<sub>2</sub>,  
30 -S(O)<sub>2</sub>-aryl, -S(O)-aryl, -S(O)<sub>2</sub>-heteroaryl,  
-S(O)-heteroaryl, -S(O)<sub>2</sub>-alkylaryl, -S(O)-alkylaryl,  
-S(O)<sub>2</sub>-alkylheteroaryl, -S(O)-alkylheteroaryl,  
-S(O)<sub>2</sub>N(H)-aryl, -S(O)N(H)-aryl, -S(O)<sub>2</sub>NH-heteroaryl,  
-S(O)NH-heteroaryl, -S(O)<sub>2</sub>N(H)-alkylaryl,  
35 -S(O)N(H)-alkylaryl, -S(O)<sub>2</sub>N(H)-alkylheteroaryl,

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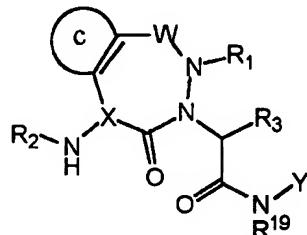
- S(O)N(H)-alkylheteroaryl, -S(O)<sub>2</sub>N(aryl)<sub>2</sub>, -S(O)N(aryl)<sub>2</sub>,
- S(O)<sub>2</sub>N(heteroaryl)<sub>2</sub>, -S(O)N(heteroaryl)<sub>2</sub>,
- S(O)<sub>2</sub>N(alkylaryl)<sub>2</sub>, -S(O)N(alkylaryl)<sub>2</sub>,
- S(O)<sub>2</sub>N(alkylheteroaryl)<sub>2</sub>, -S(O)N(alkylheteroaryl)<sub>2</sub>,
- 5 -N(H)C(O)N(H)aryl, -N(H)C(O)N(H)heteroaryl,
- N(H)C(O)N(H)alkylaryl, -N(H)C(O)N(H)alkylheteroaryl,
- N(H)C(O)N(aryl)<sub>2</sub>, -N(H)C(O)N(heteroaryl)<sub>2</sub>,
- N(H)C(O)N(alkylaryl)<sub>2</sub>, or -N(H)C(O)N(alkylheteroaryl)<sub>2</sub>;

10 R<sup>19</sup> is hydrogen; and

each R<sup>21</sup> is independently -aryl, -heteroaryl, cycloalkyl, or -heterocyclyl, wherein a hydrogen atom bound to any carbon atom is optionally replaced by R<sup>4</sup> and 15 a hydrogen atom bound to any nitrogen atom is optionally replaced by R<sup>2</sup>.

The compounds of another embodiment (B) of this invention are those of formula (II):

20



wherein:

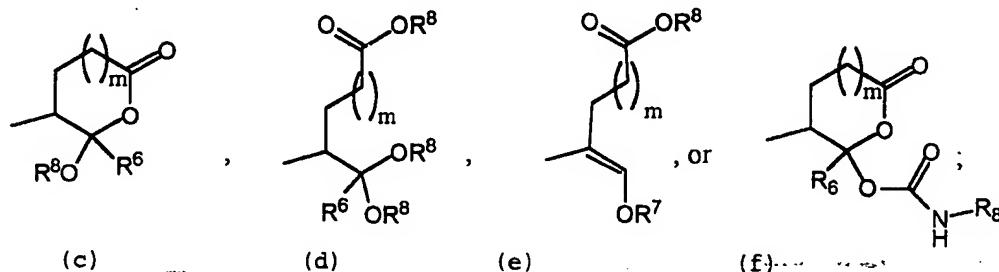
C is an aryl or heteroaryl ring, wherein any hydrogen atom bound to the C ring is optionally substituted with -R<sup>4</sup>; and

the other substituents are as described above in embodiment (A).

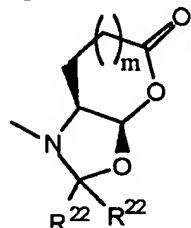
- 18 -

The compounds of two other embodiments (C) and (D) of this invention are those of formulae (I) or (II), respectively, wherein:

Y is (c), (d), (e), or (f), when R<sup>19</sup> is  
5 hydrogen:



and when R<sup>19</sup> is not hydrogen, R<sup>19</sup> and Y, together with  
10 the nitrogen atom to which they are bound, form a ring  
(g):



(g)

R<sup>7</sup> is -C(O)alkyl, -C(O)cycloalkyl,  
-C(O)alkylenyl, -C(O)alkylaryl, -C(O)alkylheteroaryl,  
15 -C(O)heterocycle, or -C(O)alkylheterocycle;

each R<sup>22</sup> is independently -H, -alkyl, -aryl,  
-heteroaryl, -cycloalkyl, -alkylaryl, or  
-alkylheteroaryl; and

20

the other substituents are as described above.

Preferably:

m is 0;

25 W is -CH<sub>2</sub>- or -C(O)-;

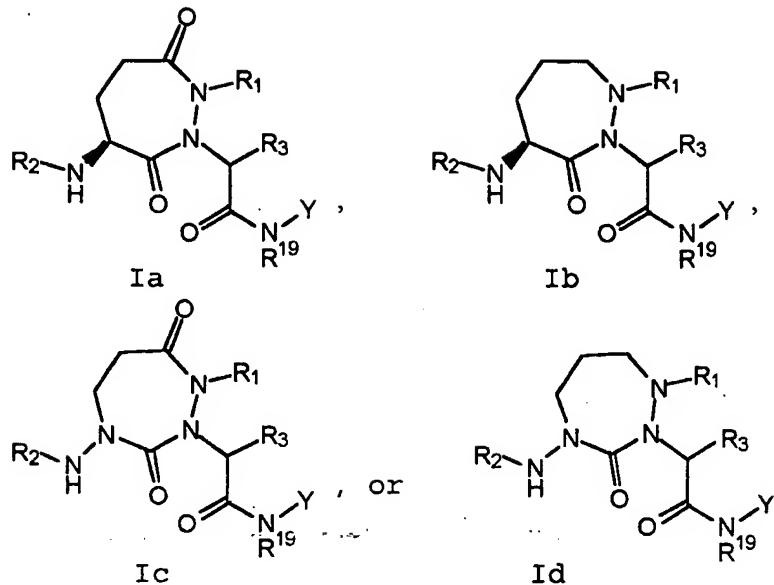
- 19 -

X is -C(H)- or -N-;  
|  
Z is -CH<sub>2</sub>-;  
R<sup>5</sup> is -OH;  
5 R<sup>6</sup> is -H or -R<sup>14</sup>;  
R<sup>7</sup> is -C(O)alkyl;  
R<sup>8</sup> is methyl, ethyl, n-propyl, isopropyl,  
cyclopentyl, phenethyl, or benzyl; or  
R<sup>9</sup> is -C(O)aryl, -C(O)heteroaryl,  
10 -C(O)alkylaryl, -C(O)alkylheteroaryl, -alkylaryl,  
-alkylheteroaryl, -aryl, or -heteroaryl;  
Q is O;  
R<sup>14</sup> is (i) substituted with -Oalkyl, -F or -Cl,  
or (ii) substituted with phenyl; or  
15 C is a benzo ring, wherein any hydrogen bound  
to the ring is optionally replaced with -R<sup>4</sup>;

More preferably, R<sup>6</sup> is -H.

20 In any of the above embodiments, preferred  
forms of formula (I) are those wherein:  
Z is -CH<sub>2</sub>-, W is -C(O)- and X is -C(H)- (Ia);  
Z is -CH<sub>2</sub>-, W is -CH<sub>2</sub>- and X is -C(H)- (Ib),  
25 Z is -CH<sub>2</sub>-, W is -C(O)- and X is -N- (Ic); or  
Z is -CH<sub>2</sub>-, W is -CH<sub>2</sub>- and X is -N- (Id);  
|

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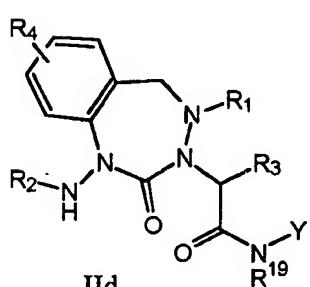
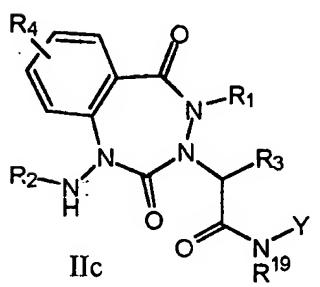
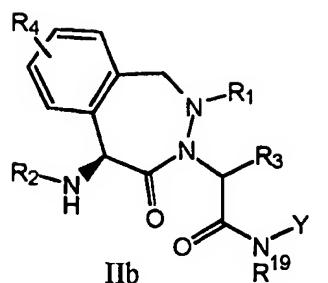
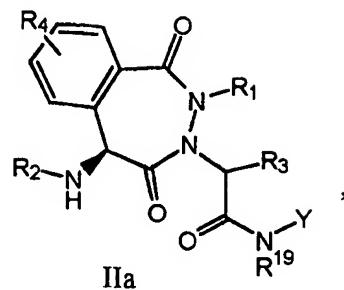
and the other substituents are as described above.

In any of the above embodiments, preferred forms of formula (II) are those wherein:

- 5        W is -C(O)- and X is -C(H)- (IIa),
- W is -CH<sub>2</sub>- and X is -C(H)- (IIb),
- W is -C(O)- and X is -N- (IIc), or
- 10      W is -CH<sub>2</sub>- and X is -N- (IId); and

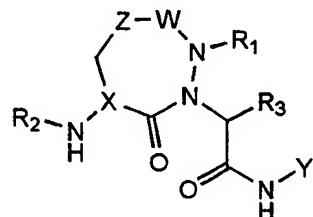
C is a benzo ring, wherein any hydrogen bound to the ring is optionally substituted with -R<sup>4</sup>:

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and the other substituents are as described above.

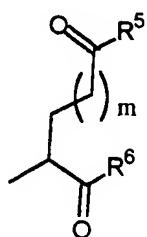
The compounds of a preferred embodiment (E) of  
5 this invention are those of formula (I):



wherein:

Y is:

(a)

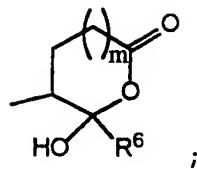


10

or

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(b)



m is 0 or 1;

5

W is -CH<sub>2</sub>- , -C(O)- , S(O)<sub>2</sub> , or -S(O)- ;X is -C(H)- , -C(R<sup>8</sup>)- , or -N- ;

10

Z is -CH<sub>2</sub>- , -O- , -S- , or -N(R<sup>1</sup>)- , provided that  
if Z is -N(R<sup>1</sup>)- , then W is -C(O)- , -S(O)<sub>2</sub>- , or -S(O)- ;each R<sup>1</sup> is independently -H, -C(O)R<sup>8</sup>, -S(O)<sub>2</sub>R<sup>8</sup>,  
15 -S(O)R<sup>8</sup>, -R<sup>21</sup>, -alkyl-R<sup>21</sup>, -alkenyl-R<sup>21</sup>, -alkynyl-R<sup>21</sup>,  
-alkyl;R<sup>2</sup> is -C(O)R<sup>8</sup>, -C(O)C(O)R<sup>8</sup>, -S(O)<sub>2</sub>R<sup>8</sup>, -S(O)R<sup>8</sup>,  
-C(O)OR<sup>8</sup>, -C(O)N(H)R<sup>8</sup>, -S(O)<sub>2</sub>N(H)-R<sup>8</sup>, -S(O)N(H)-R<sup>8</sup>,  
20 -C(O)C(O)N(H)R<sup>8</sup>, -C(O)CH=CHR<sup>8</sup>, -C(O)CH<sub>2</sub>OR<sup>8</sup>,  
-C(O)CH<sub>2</sub>N(H)R<sup>8</sup> , -C(O)N(R<sup>8</sup>)<sub>2</sub>, -S(O)<sub>2</sub>N(R<sup>8</sup>)<sub>2</sub>, -S(O)N(R<sup>8</sup>)<sub>2</sub>,  
-C(O)C(O)N(R<sup>8</sup>)<sub>2</sub>, -C(O)CH<sub>2</sub>N(R<sup>8</sup>)<sub>2</sub>, -CH<sub>2</sub>-R<sup>8</sup>,  
-CH<sub>2</sub>-alkenyl-R<sup>8</sup>, or -CH<sub>2</sub>-alkynyl-R<sup>8</sup>;25 R<sup>3</sup> is -H, -R<sup>21</sup>, -alkyl-R<sup>21</sup>, -alkenyl-R<sup>21</sup>,  
-alkynyl-R<sup>21</sup>, alkyl, or an amino acid side chain;each R<sup>4</sup> is independently -OH, -F, -Cl, -Br, -I,  
-NO<sub>2</sub>, -CN, -NH<sub>2</sub>, -CO<sub>2</sub>H, -C(O)NH<sub>2</sub>, -N(H)C(O)H,  
30 -N(H)C(O)NH<sub>2</sub>, -alkyl, -cycloalkyl, -perfluoroalkyl,  
-O-alkyl, -N(H)alkyl, -N(alkyl)<sub>2</sub>, -C(O)N(H)alkyl,  
-C(O)N(alkyl)<sub>2</sub>, -N(H)C(O)alkyl, -N(H)C(O)N(H)alkyl,

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-N(H)C(O)N(alkyl)<sub>2</sub>, -S-alkyl, -S(O)<sub>2</sub>alkyl, -S(O)alkyl,  
 -C(O)alkyl, -CH<sub>2</sub>NH<sub>2</sub>, -CH<sub>2</sub>N(H)alkyl, -CH<sub>2</sub>N(alkyl)<sub>2</sub>, or  
 -N(H)C(O)Oalkyl;

5           R<sup>5</sup> is -OH, -OR<sup>8</sup>, -N(H)OH, or -N(H)SO<sub>2</sub>R<sup>8</sup>;

R<sup>6</sup> is -H, -CH<sub>2</sub>OR<sup>9</sup>, -CH<sub>2</sub>SR<sup>10</sup>, -CH<sub>2</sub>N(H)R<sup>9</sup>,  
 -CH<sub>2</sub>N(R<sup>9</sup>)R<sup>11</sup>, -C(H)N<sub>2</sub>, -CH<sub>2</sub>F, -CH<sub>2</sub>Cl, -CH<sub>2</sub>Br, -CH<sub>2</sub>I,  
 -C(O)N(R<sup>11</sup>)<sub>2</sub>, -R<sup>13</sup>, or -R<sup>14</sup>;

10           each R<sup>8</sup> is independently -alkyl, -cycloalkyl,  
 -aryl, -heteroaryl, -heterocyclyl, -alkylcycloalkyl  
 -alkylaryl, -alkylheteroaryl, or -alkylheterocyclyl;

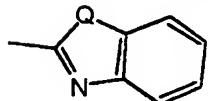
15           R<sup>9</sup> is -H, -C(O)aryl, -C(O)heteroaryl,  
 -C(O)alkylaryl, -C(O)alkylheteroaryl, -alkylaryl,  
 -alkylheteroaryl, -aryl, -heteroaryl, or -P(O)(R<sup>15</sup>)<sub>2</sub>;

R<sup>10</sup> is -alkylaryl or -alkylheteroaryl;

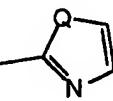
20           each R<sup>11</sup> is independently -H, -alkyl, -aryl,  
 -heteroaryl, -cycloalkyl, -alkylaryl, or  
 -alkylheteroaryl;

25           R<sup>13</sup> is -alkylaryl or -alkylheteroaryl;

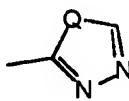
R<sup>14</sup> is



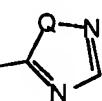
(i)



(ii)



(iii)



(iv)

30           wherein Q is -O- or -S-, any hydrogen atom in (i)  
 is optionally replaced with -R<sup>17</sup>, and any hydrogen atom  
 in (ii), (iii), and (iv) is optionally replaced with  
 -R<sup>17</sup>, -R<sup>18</sup> or -alkyl-R<sup>18</sup>;

each R<sup>15</sup> is independently -H, -OH, -alkyl,  
-aryl, -heteroaryl, -cycloalkyl, -alkylaryl,  
-alkylheteroaryl, -Oalkyl, -Oaryl, -Oheteroaryl,  
-Oalkylaryl, or -Oalkylheteroaryl;

5

each R<sup>17</sup> is independently -OH, -F, -Cl, -Br,  
-I, -NO<sub>2</sub>, -CN, -NH<sub>2</sub>, -CO<sub>2</sub>H, -C(O)NH<sub>2</sub>, -N(H)C(O)H,  
-N(H)C(O)NH<sub>2</sub>, -SO<sub>2</sub>NH<sub>2</sub>, -C(O)H, -alkyl, -cycloalkyl,  
-perfluoroalkyl, -O-alkyl, -N(H)alkyl, -N(alkyl)<sub>2</sub>,  
-CO<sub>2</sub>alkyl, -C(O)N(H)alkyl, -C(O)N(alkyl)<sub>2</sub>,  
-N(H)C(O)alkyl, -N(H)C(O)N(H)alkyl, -N(H)C(O)N(alkyl)<sub>2</sub>,  
-S(O)<sub>2</sub>N(H)alkyl, -S(O)N(H)alkyl, -S(O)<sub>2</sub>N(alkyl)<sub>2</sub>,  
-S(O)N(alkyl)<sub>2</sub>, -S-alkyl, -S(O)<sub>2</sub>alkyl, -S(O)alkyl, or  
-C(O)alkyl;

10

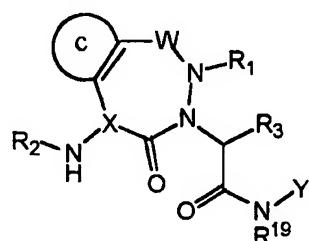
each R<sup>18</sup> is independently -aryl, -heteroaryl,  
-alkylaryl, -alkylheteroaryl, -O-aryl, -O-heteroaryl,  
-O-alkylaryl, -O-alkylheteroaryl, -N(H)aryl, -N(aryl)<sub>2</sub>,  
-N(H)heteroaryl, -N(heteroaryl)<sub>2</sub>, -N(H)alkylaryl,  
-N(alkylaryl)<sub>2</sub>, -N(H)alkylheteroaryl,  
-N(alkylheteroaryl)<sub>2</sub>, -S-aryl, -S-heteroaryl,  
-S-alkylaryl, -S-alkylheteroaryl, -C(O)aryl,  
-C(O)heteroaryl, -C(O)alkylaryl, -C(O)alkylheteroaryl,  
-CO<sub>2</sub>aryl, -CO<sub>2</sub>heteroaryl, -CO<sub>2</sub>alkylaryl,  
-CO<sub>2</sub>alkylheteroaryl, -C(O)N(H)aryl, -C(O)N(aryl)<sub>2</sub>,  
-C(O)N(H)heteroaryl, -C(O)N(heteroaryl)<sub>2</sub>,  
-C(O)N(H)alkylaryl, -C(O)N(alkylaryl)<sub>2</sub>,  
-C(O)N(H)alkylheteroaryl, -C(O)N(alkylheteroaryl)<sub>2</sub>,  
-S(O)<sub>2</sub>-aryl, -S(O)-aryl, -S(O)<sub>2</sub>-heteroaryl,  
-S(O)-heteroaryl, -S(O)<sub>2</sub>-alkylaryl, -S(O)-alkylaryl,  
-S(O)<sub>2</sub>N(H)-aryl, -S(O)N(H)-aryl, -S(O)<sub>2</sub>NH-heteroaryl,  
-S(O)NH-heteroaryl, -S(O)<sub>2</sub>N(H)-alkylaryl,  
-S(O)N(H)-alkylaryl, -S(O)<sub>2</sub>N(H)-alkylheteroaryl,  
-S(O)N(H)-alkylheteroaryl, -S(O)<sub>2</sub>N(aryl)<sub>2</sub>, -S(O)N(aryl)<sub>2</sub>,

- 25 -

$-S(O)_2N(\text{heteroaryl})_2$ ,  $-S(O)N(\text{heteroaryl})_2$ ,  
 $-S(O)_2N(\text{alkylaryl})_2$ ,  $-S(O)N(\text{alkylaryl})_2$ ,  
 $-S(O)_2N(\text{alkylheteroaryl})_2$ ,  $-S(O)N(\text{alkylheteroaryl})_2$ ,  
 $-N(H)C(O)N(H)\text{aryl}$ ,  $-N(H)C(O)N(H)\text{heteroaryl}$ ,  
5       $-N(H)C(O)N(H)\text{alkylaryl}$ ,  $-N(H)C(O)N(H)\text{alkylheteroaryl}$ ,  
 $-N(H)C(O)N(\text{aryl})_2$ ,  $-N(H)C(O)N(\text{heteroaryl})_2$ ,  
 $-N(H)C(O)N(\text{alkylaryl})_2$ , or  $-N(H)C(O)N(\text{alkylheteroaryl})_2$ ;  
and

10      each  $R^{21}$  is independently -aryl, -heteroaryl,  
cycloalkyl, or -heterocyclyl, wherein a hydrogen atom  
bound to any carbon atom is optionally replaced by  $R^4$  and  
a hydrogen atom bound to any nitrogen atom is optionally  
replaced by  $R^2$ .

15      The compounds of another preferred embodiment  
(F) of this invention are those of formula (II):



20      wherein:

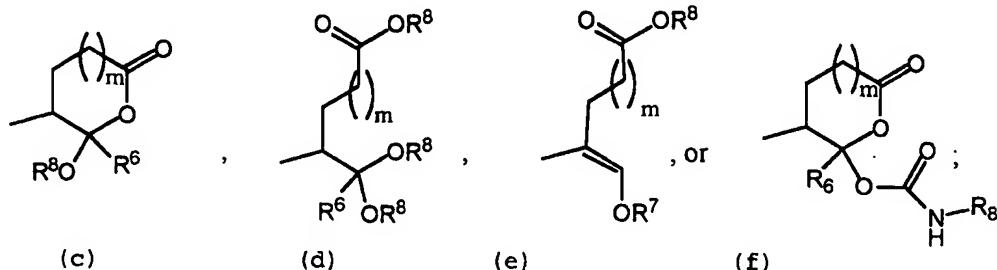
C is an aryl or heteroaryl ring, wherein any  
hydrogen atom bound to the C ring is optionally  
substituted with  $-R^4$ ; and

25      the other substituents are as described above  
in embodiment (E).

The compounds of two other embodiments (G) and (H) of this invention are those of formulae (I) or (II), respectively, wherein:

Y is (c), (d), (e), or (f):

5



10      R<sup>7</sup> is -C(O)alkyl, -C(O)cycloalkyl,  
 -C(O)alkylenyl, -C(O)alkylaryl, -C(O)alkylheteroaryl,  
 -C(O)heterocycle, or -C(O)alkylheterocycle; and

the other substituents are as described above.  
 Preferably:

15      m is 0;

W is -CH<sub>2</sub>- or -C(O)-;

X is -C(H)- or -N-;

Z is -CH<sub>2</sub>-;

20      R<sup>5</sup> is -OH;

R<sup>6</sup> is -H, -R<sup>14</sup>, -CH<sub>2</sub>OR<sup>9</sup> or -CH<sub>2</sub>F;

R<sup>7</sup> is -C(O)alkyl;

R<sup>8</sup> is methyl, ethyl, n-propyl, isopropyl,  
 cyclopentyl, phenethyl, or benzyl;

25      R<sup>9</sup> is -C(O)aryl, -C(O)heteroaryl,

-C(O)alkylaryl, -C(O)alkylheteroaryl, -alkylaryl,  
 -alkylheteroaryl, -aryl, or -heteroaryl;

Q is O;

30      R<sup>14</sup> is (i) substituted with -Oalkyl, -F or -Cl,  
 or (ii) substituted with phenyl;

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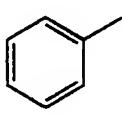
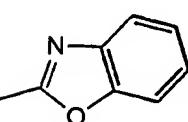
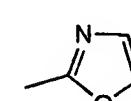
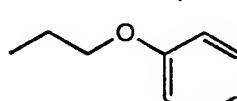
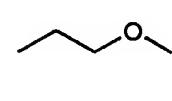
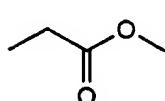
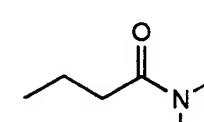
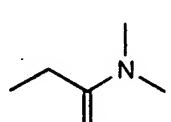
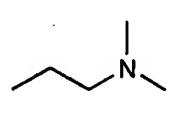
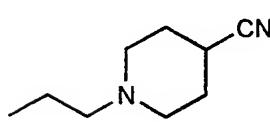
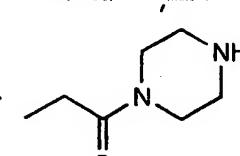
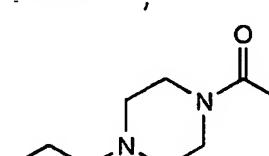
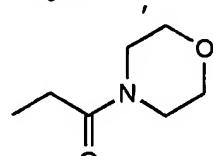
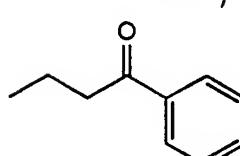
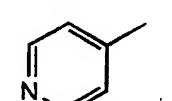
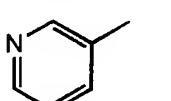
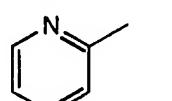
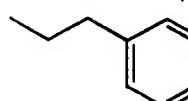
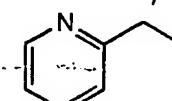
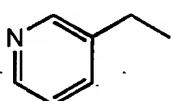
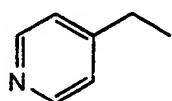
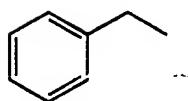
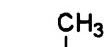
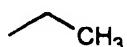
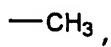
C is a benzo ring, wherein any hydrogen bound to the ring is optionally replaced with -R<sup>4</sup>;

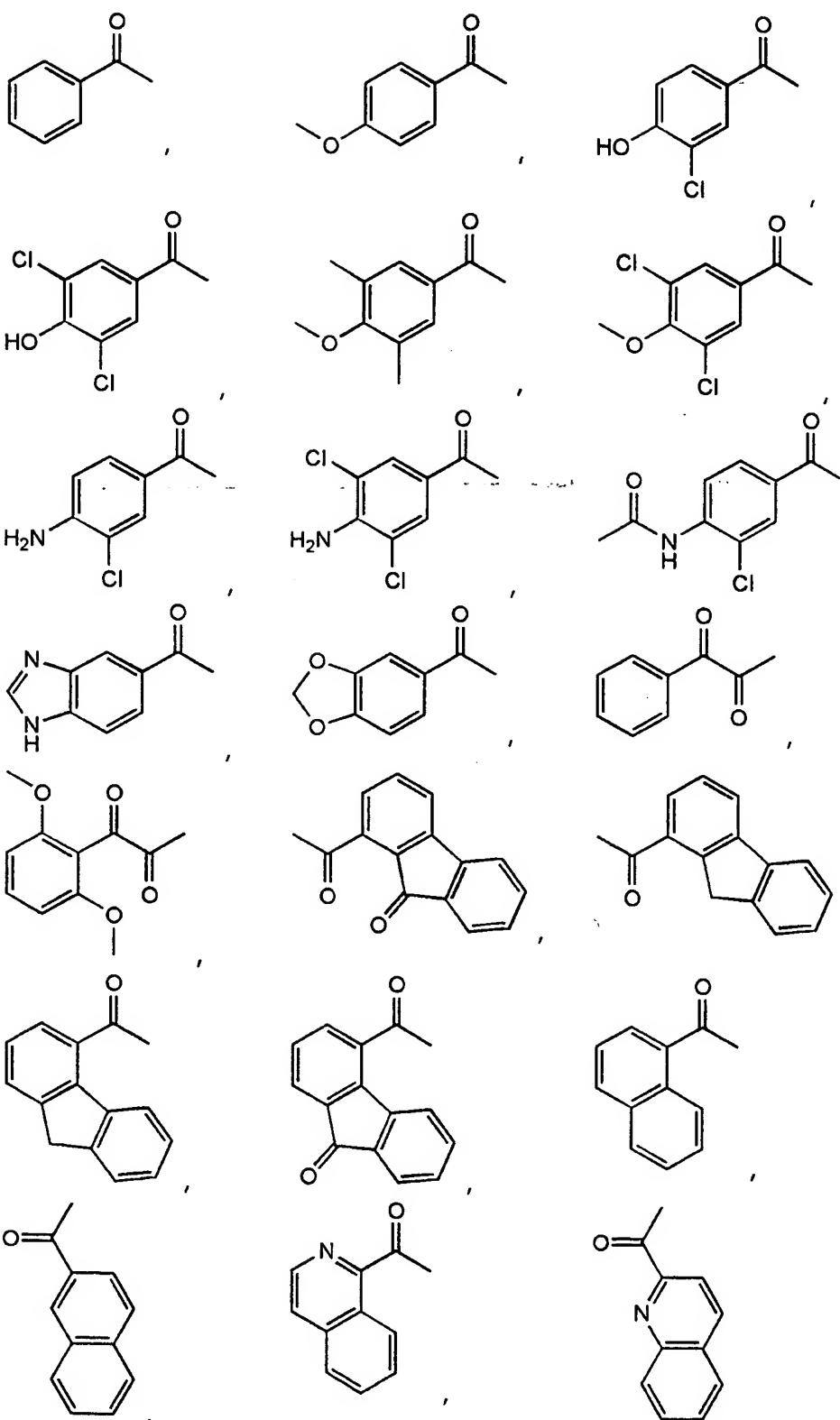
R<sup>1</sup> is aryl, heteroaryl, alkyl, alkylaryl, or alkylheteroaryl; or

5 R<sup>3</sup> is an amino acid side chain, aryl, heteroaryl, alkyl, alkylaryl, or alkylheteroaryl.

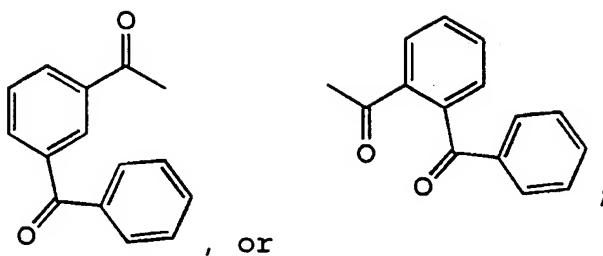
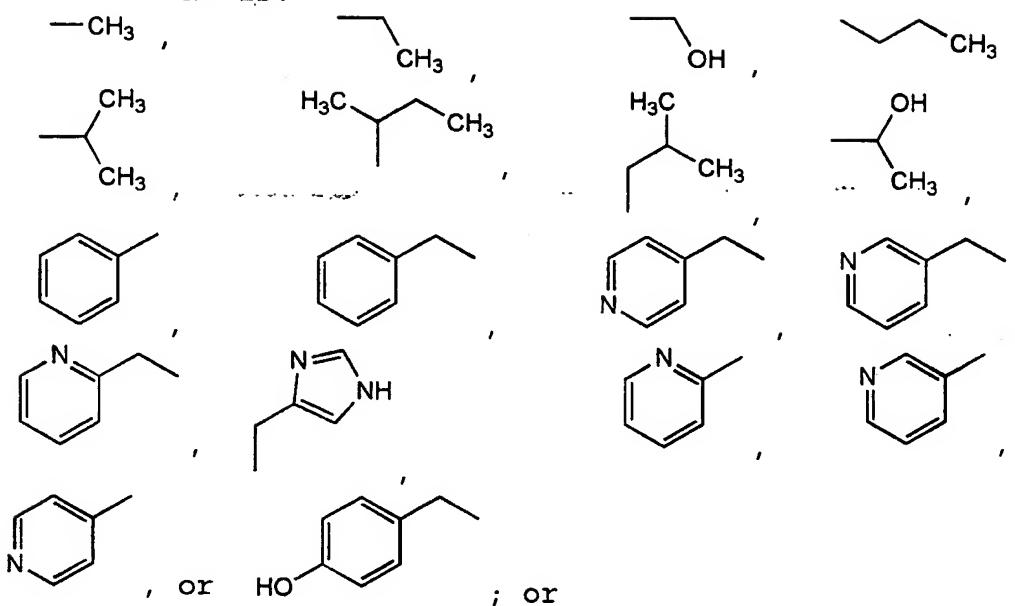
More preferably,

R<sup>1</sup> is:



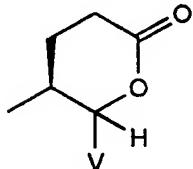


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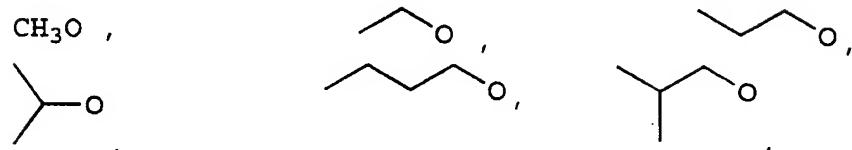
 $R^3$  is: $R^6$  is  $-H$ .

5

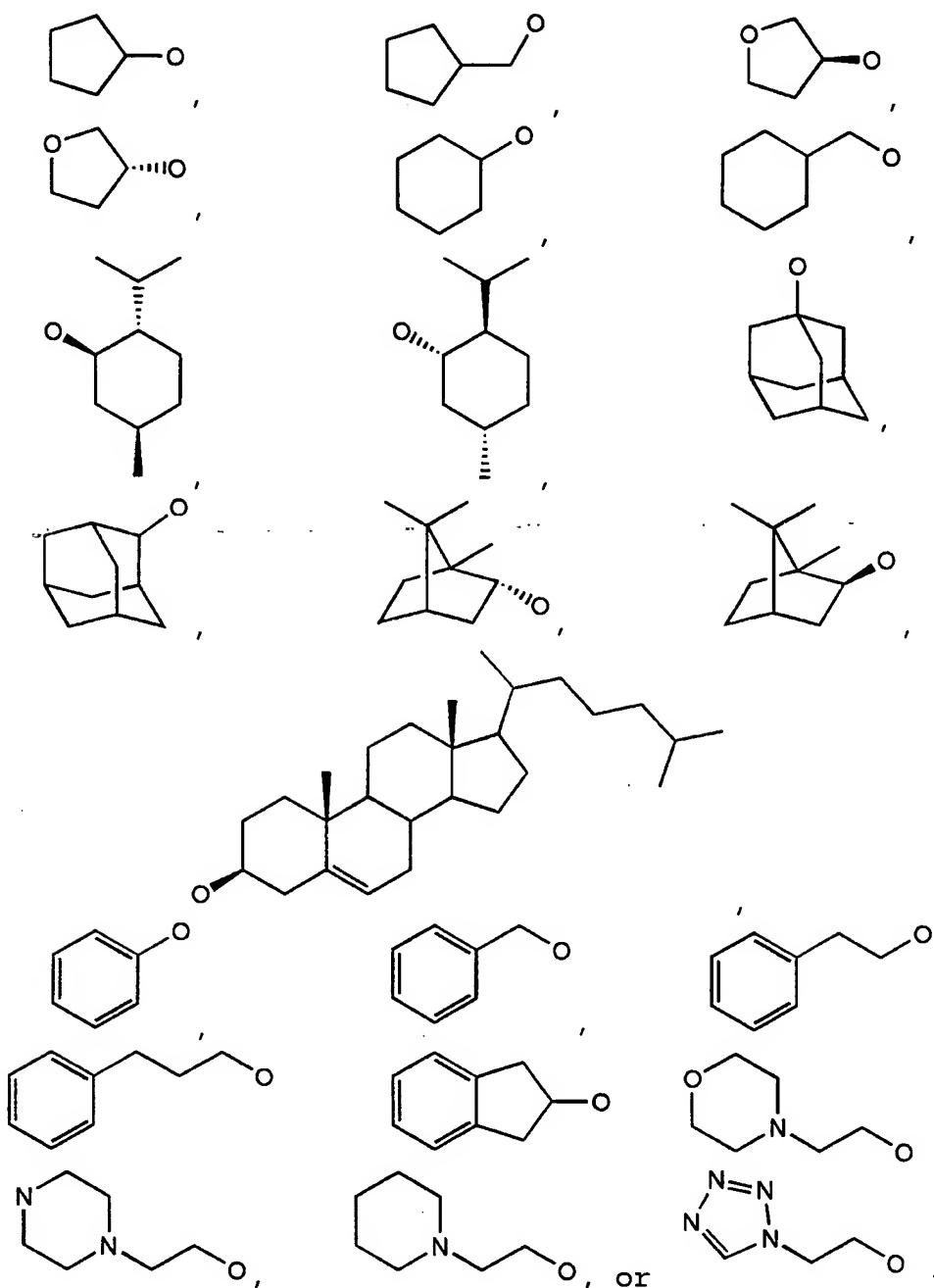
In embodiments (C), (D), (G), or (H) Y is:

 $; \text{ and } V \text{ is preferably:}$ 

15



- 30 -



In any of the above embodiments, preferred forms of formula (I) are those wherein:

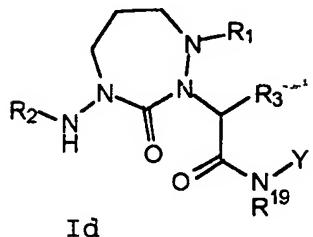
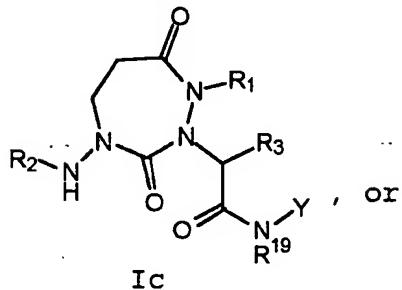
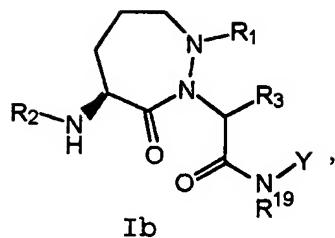
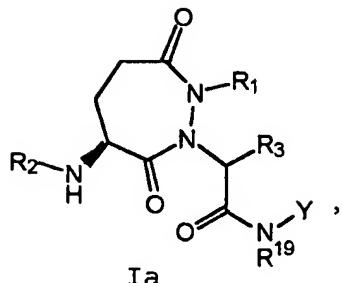
Z is -CH<sub>2</sub>- , W is -C(O)- and X is -C(H)- (Ia);

Z is -CH<sub>2</sub>- , W is -CH<sub>2</sub>- and X is -C(H)- (Ib),

Z is -CH<sub>2</sub>- , W is -C(O)- and X is -N- (Ic); or

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Z is -CH<sub>2</sub>- , W is -CH<sub>2</sub>- and X is -N- (Id):

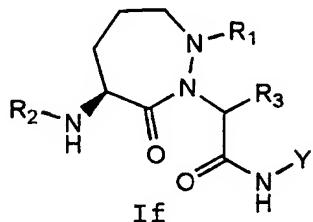
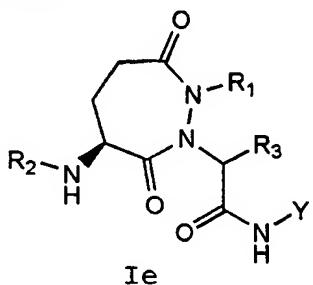


5

and the other substituents are as described above.

More preferred forms of formula (I) are as follows:

10



20

In any of the above embodiments, preferred forms of formula (II) are those wherein:

25

W is  $-C(O)-$  and X is  $-C(H)-$  (IIa),

W is  $-\text{CH}_2-$  and X is  $-\text{C}(\text{H})-$  (IIb),

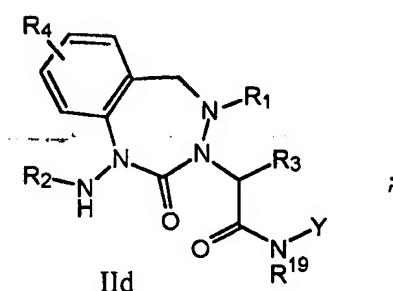
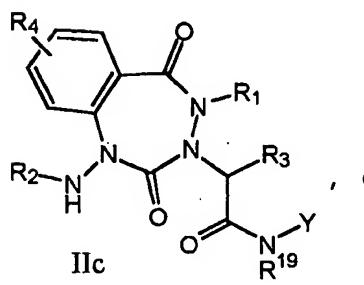
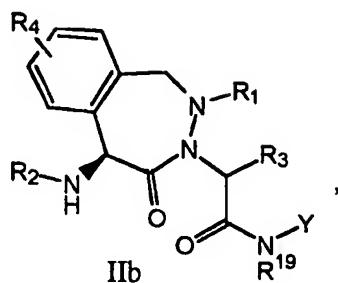
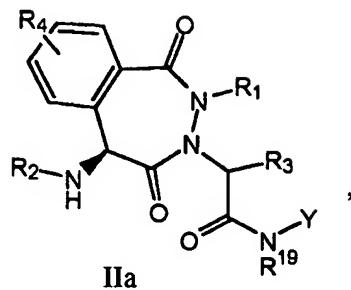
W is  $-C(O)-$  and X is  $-N-$  (IIc), or

30

W is  $\text{-CH}_2\text{-}$  and X is  $\text{-N-}$  (IIId); and

C is a benzene ring, wherein any hydrogen bound to the ring is optionally substituted with -R<sup>4</sup>:

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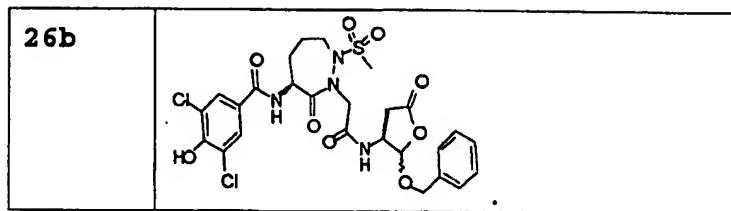


and the other substituents are as described above.

Specific compounds of this invention include,  
5 but are not limited to:

IIa	<p>Chemical structure of compound IIa: A tricyclic compound consisting of a quinoline ring fused to a pyrrolidine ring, which is further fused to a pyrazine ring. The pyrazine ring has an R<sub>4</sub> substituent at position 2 and an R<sub>1</sub> substituent at position 4. The pyrrolidine ring has an R<sub>2</sub>-NH group at position 2 and an R<sub>3</sub> substituent at position 5. The quinoline ring has an R<sub>18</sub>-N(Y)C(=O)R<sub>19</sub> substituent at position 3. The structure shown is for R<sub>4</sub> = phenyl, R<sub>1</sub> = methyl, R<sub>2</sub> = ethyl, R<sub>3</sub> = isobutyl, R<sub>18</sub> = isopropyl, Y = phenyl, and R<sub>19</sub> = methyl.</p>
IIb	<p>Chemical structure of compound IIb: A tricyclic compound consisting of a quinoline ring fused to a pyrrolidine ring, which is further fused to a pyrazine ring. The pyrazine ring has an R<sub>4</sub> substituent at position 2 and an R<sub>1</sub> substituent at position 4. The pyrrolidine ring has an R<sub>2</sub>-NH group at position 2 and an R<sub>3</sub> substituent at position 5. The quinoline ring has an R<sub>18</sub>-N(Y)C(=O)R<sub>19</sub> substituent at position 3. The structure shown is for R<sub>4</sub> = phenyl, R<sub>1</sub> = methyl, R<sub>2</sub> = ethyl, R<sub>3</sub> = isobutyl, R<sub>18</sub> = isopropyl, Y = phenyl, and R<sub>19</sub> = methyl.</p>

11c	
20	
27	
10a	
10b	
19	



The compounds of this invention may contain one or more "asymmetric" carbon atoms and thus may occur as 5 racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. Each stereogenic carbon may be of the R or S configuration. Although specific compounds and scaffolds exemplified in this application may be depicted in a 10 particular stereochemical configuration, compounds and scaffolds having either the opposite stereochemistry at any given chiral center or mixtures thereof are also envisioned.

All such isomeric forms of these compounds are 15 expressly included in the present invention, as well as pharmaceutically acceptable derivative thereof.

The term "pharmaceutically acceptable derivative" means any pharmaceutically acceptable salt, ester, or salt of such ester, of a compound of this 20 invention or any other compound which, upon administration to a recipient, is capable of providing (directly or indirectly) a compound of this invention or an anti-ICE active metabolite or residue thereof.

Pharmaceutically acceptable salts of the 25 compounds of this invention include, for example, those derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acids include hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycolic, lactic, salicylic, succinic, toluene-p-sulfonic, 30 tartaric, acetic, citric, methanesulfonic, formic,

benzoic, malonic, naphthalene-2-sulfonic and benzenesulfonic acids. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as  
5 intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable acid addition salts. Salts derived from appropriate bases include alkali metal (e.g., sodium), alkaline earth metal (e.g., magnesium), ammonium and N-(C<sub>1-4</sub> alkyl)<sub>4</sub><sup>+</sup> salts.

10 This invention also envisions the "quaternization" of any basic nitrogen-containing groups of the compounds disclosed herein. The basic nitrogen can be quaternized with any agents known to those of ordinary skill in the art including, for example, lower  
15 alkyl halides, such as methyl, ethyl, propyl and butyl chloride, bromides and iodides; dialkyl sulfates including dimethyl, diethyl, dibutyl and diamyl sulfates; long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides; and aralkyl  
20 halides including benzyl and phenethyl bromides. Water or oil-soluble or dispersible products may be obtained by such quaternization.

When multiply substituted, each substituent may be picked independently of any other substituent as long  
25 as the combination of substituents results in the formation of a stable compound.

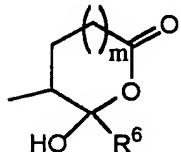
Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds. The term "stable",  
30 as used herein, refers to compounds which possess stability sufficient to allow manufacture and administration to a mammal by methods known in the art. Typically, such compounds are stable at a temperature of 40 °C or less, in the presence or absence of moisture or

other chemically reactive conditions, for at least a week.

Preferred compounds of this invention may be readily absorbed by the bloodstream of patients upon oral administration. This oral availability makes such compounds excellent agents for orally-administered treatment and prevention regimens against IL-1-, apoptosis-, IGIF-, or IFN- $\gamma$ -mediated diseases.

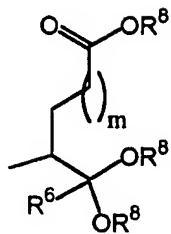
It should be understood that the compounds of this invention may exist in various equilibrium forms, depending on conditions including choice of solvent, pH, and others known to the practitioner skilled in the art. All such forms of these compounds are expressly included in the present invention. In particular, many of the compounds of this invention, especially those which contain aldehyde or ketone groups and carboxylic acid groups in Y, may take hemi-acetal or hemi-ketal or hydrated forms. For example, compounds of embodiment (A) are in a hemi-acetal or hemi-ketal form when Y is:

20

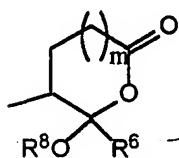


Depending on the choice of solvent and other conditions known to the practitioner skilled in the art, compounds of this invention may also take hydrated, acyloxy ketal, acyloxy acetal, ketal, acetal or enol forms. For example, compounds of this invention are in hydrated forms when Y is:

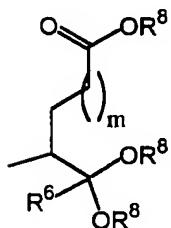
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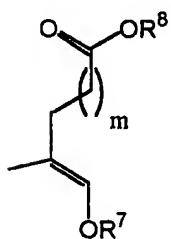
acyloxy ketal or acyloxy acetal forms when Y is:



ketal or acetal forms when Y is:



and enol forms when Y is:



In addition, it should be understood that the equilibrium forms of the compounds of this invention may include tautomeric forms. All such forms of these

compounds are expressly included in the present invention.

The compounds of formulae (I) and (II) may be synthesized using conventional techniques.

5 Advantageously, these compounds are conveniently synthesized from readily available starting materials.

The compounds of this invention are among the most readily synthesized caspase inhibitors known. Many of the previously described caspase or ICE inhibitors 10 contain four or more chiral centers and numerous peptide linkages. The relative ease with which the compounds of this invention can be synthesized represents an advantage in the large scale production of these compounds.

For example, compounds of this invention may be 15 prepared using the processes described herein. As can be appreciated by the skilled practitioner, these processes are not the only means by which the compounds described and claimed in this application may be synthesized. Further methods will be evident to those of ordinary 20 skill in the art. Additionally, the various synthetic steps described herein may be performed in an alternate sequence or order to give the desired compounds.

It should be understood that the compounds of this invention may be modified by appropriate 25 functionalities to enhance selective biological properties. Such modifications are known in the art and include those which increase biological penetration into a given biological system (e.g., blood, lymphatic system, central nervous system), increase oral availability, 30 increase solubility to allow administration by injection, alter metabolism and alter rate of excretion. In addition, the compounds may be altered to pro-drug form such that the desired compound is created in the body of the patient as the result of the action of metabolic or 35 other biochemical processes on the pro-drug. Such pro-

drug forms typically demonstrate little or no activity in in vitro assays. Some examples of pro-drug forms include ketal, acetal, oxime, imine and hydrazone forms of compounds which contain ketone or aldehyde groups,  
5 especially where they occur in the Y group of the compounds of this invention. Other examples of pro-drug forms include the hemi-ketal, hemi-acetal, acyloxy ketal, acyloxy acetal, ketal, acetal and enol forms that are described herein.

10

#### Compositions and Methods

The compounds of this invention are caspase inhibitors, particularly ICE inhibitors. Accordingly, these compounds are capable of targeting and inhibiting events in IL-1-, apoptosis-, IGIF-, and IFN- $\gamma$ -mediated diseases, and, thus, the ultimate activity of that protein in inflammatory diseases, autoimmune diseases, destructive bone, proliferative disorders, infectious diseases, and degenerative diseases. For example, the  
15 compounds of this invention inhibit the conversion of precursor IL-1 $\beta$  to mature IL-1 $\beta$  by inhibiting ICE. Because ICE is essential for the production of mature IL-1, inhibition of that enzyme effectively blocks initiation of IL-1-mediated physiological effects and  
20 symptoms, such as inflammation, by inhibiting the production of mature IL-1. Thus, by inhibiting IL-1 $\beta$  precursor activity, the compounds of this invention effectively function as IL-1 inhibitors.  
25

Compounds of this invention also inhibit  
30 conversion of pro-IGIF into active, mature IGIF by inhibiting ICE. Because ICE is essential for the production of mature IGIF, inhibition of ICE effectively blocks initiation of IGIF-mediated physiological effects and symptoms, by inhibiting production of mature IGIF.  
35 IGIF is in turn essential for the production of IFN- $\gamma$ . ICE

therefore effectively blocks initiation of IFN- $\gamma$ - mediated physiological effects and symptoms, by inhibiting production of mature IGIF and thus production of IFN- $\gamma$ .

The pharmaceutical compositions and methods of  
5 this invention, therefore, will be useful for controlling caspase activity in vivo. The compositions and methods of this invention will thus be useful for controlling IL-1, IGIF or IFN- $\gamma$  levels in vivo and for treating or reducing the advancement, severity or effects of IL-1-,  
10 apoptosis-, IGIF-, or IFN- $\gamma$ -mediated conditions, including diseases, disorders or effects.

Pharmaceutical compositions of this invention comprise a compound of formulae (I) or (II) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier. Such compositions may optionally comprise an additional therapeutic agent. Such agents include, but are not limited to, an anti-inflammatory agent, a matrix metalloprotease inhibitor, a lipoxygenase inhibitor, a cytokine antagonist, an  
15 immunosuppressant, an anti-cancer agent, an anti-viral agent, a cytokine, a growth factor, an immunomodulator, a prostaglandin or an anti-vascular hyperproliferation compound.  
20

The term "pharmaceutically acceptable carrier" refers to a non-toxic carrier that may be administered to a patient, together with a compound of this invention, and which does not destroy the pharmacological activity thereof.  
25

Pharmaceutically acceptable carriers that may be used in the pharmaceutical compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated  
30  
35

vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, wool fat and self-emulsifying drug delivery systems (SEDDS) such as  $\alpha$ -tocopherol, polyethyleneglycol 1000 succinate, or other similar polymeric delivery matrices.

In pharmaceutical composition comprising only a compound of formulae (I) or (II) as the active component, methods for administering these compositions may additionally comprise the step of administering to the subject an additional agent. Such agents include, but are not limited to, an anti-inflammatory agent, a matrix metalloprotease inhibitor, a lipoxygenase inhibitor, a cytokine antagonist, an immunosuppressant, an anti-cancer agent, an anti-viral agent, a cytokine, a growth factor, an immunomodulator, a prostaglandin or an anti-vascular hyperproliferation compound.

The term "pharmaceutically effective amount" refers to an amount effective in treating or ameliorating an IL-1-, apoptosis-, IGIF- or IFN- $\gamma$ -mediated disease in a patient. The term "prophylactically effective amount" refers to an amount effective in preventing or substantially lessening IL-1-, apoptosis-, IGIF- or IFN- $\gamma$ -mediated diseases in a patient.

The compounds of this invention may be employed in a conventional manner for controlling IGIF and IFN- $\gamma$  levels in vivo and for treating diseases or reducing the advancement or severity of effects which are mediated by IL-1, apoptosis, IGIF or IFN- $\gamma$ . Such methods of treatment, their dosage levels and requirements may be

selected by those of ordinary skill in the art from available methods and techniques.

For example, a compound of this invention may be combined with a pharmaceutically acceptable adjuvant 5 for administration to a patient suffering from an IL-1-, apoptosis-, IGIF- or IFN- $\gamma$ -mediated disease in a pharmaceutically acceptable manner and in an amount effective to lessen the severity of that disease.

Alternatively, the compounds of this invention 10 may be used in compositions and methods for treating or protecting individuals against IL-1, apoptosis-, IGIF, or IFN- $\gamma$  mediated diseases over extended periods of time. The compounds may be employed in such compositions either alone or together with other compounds of this invention 15 in a manner consistent with the conventional utilization of enzyme inhibitors in pharmaceutical compositions. For example, a compound of this invention may be combined with pharmaceutically acceptable adjuvants conventionally employed in vaccines and administered in prophylactically 20 effective amounts to protect individuals over an extended period of time against IL-1-, apoptosis-, IGIF, or IFN- $\gamma$  mediated diseases.

The compounds of formulae (I) or (II) may also 25 be co-administered with other caspase or ICE inhibitors to increase the effect of therapy or prophylaxis against various IL-1-, apoptosis-, IGIF- or IFN- $\gamma$  mediated diseases.

In addition, the compounds of this invention 30 may be used in combination either conventional anti-inflammatory agents or with matrix metalloprotease inhibitors, lipoxygenase inhibitors and antagonists of cytokines other than IL-1 $\beta$ .

The compounds of this invention can also be 35 administered in combination with immunomodulators (e.g., bropirimine, anti-human alpha-interferon antibody, IL-2,

GM-CSF, methionine enkephalin, interferon-alpha, diethyldithiocarbamate, tumor necrosis factor, naltrexone and EPO), with prostaglandins, or with antiviral agents (e.g., 3TC, polysulfated polysaccharides, ganciclovir, 5 ribavirin, acyclovir, alpha interferon, trimethotrexate and fancyclovir) or prodrugs of these or related compounds to prevent or combat IL-1-mediated disease symptoms such as inflammation.

When the compounds of this invention are 10 administered in combination therapies with other agents, they may be administered sequentially or concurrently to the patient. Alternatively, pharmaceutical or prophylactic compositions according to this invention comprise a combination of a compound of formula (I) or 15 (II) and another therapeutic or prophylactic agent.

The pharmaceutical compositions of this invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. We prefer oral 20 administration. The pharmaceutical compositions of this invention may contain any conventional non-toxic pharmaceutically-acceptable carriers, adjuvants or vehicles. In some cases, the pH of the formulation may be adjusted with pharmaceutically acceptable acids, bases 25 or buffers to enhance the stability of the formulated compound or its delivery form. The term parenteral as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intra-articular, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

The pharmaceutical compositions may be in the form of a sterile injectable preparation, for example, as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques 30 known in the art using suitable dispersing or wetting 35

agents (such as, for example, Tween 80) and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, 5 as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be 10 employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as 15 olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, such as those described in Pharmacopeia Helvetica, or a similar alcohol.

20 The pharmaceutical compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, and aqueous suspensions and solutions. In the case of tablets for oral use, carriers which are 25 commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are administered 30 orally, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

35 The pharmaceutical compositions of this invention may also be administered in the form of

suppositories for rectal administration. These compositions can be prepared by mixing a compound of this invention with a suitable non-irritating excipient which is solid at room temperature but liquid at the rectal 5 temperature and therefore will melt in the rectum to release the active components. Such materials include, but are not limited to, cocoa butter, beeswax and polyethylene glycols.

Topical administration of the pharmaceutical 10 compositions of this invention is especially useful when the desired treatment involves areas or organs readily accessible by topical application. For application topically to the skin, the pharmaceutical composition should be formulated with a suitable ointment containing 15 the active components suspended or dissolved in a carrier. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petroleum, white petroleum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, the 20 pharmaceutical composition can be formulated with a suitable lotion or cream containing the active compound suspended or dissolved in a carrier. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water. The pharmaceutical compositions of this invention may also be 25 topically applied to the lower intestinal tract by rectal suppository formulation or in a suitable enema formulation. Topically-administered transdermal patches 30 are also included in this invention.

The pharmaceutical compositions of this 35 invention may be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical

formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

5 Dosage levels of between about 0.01 and about 100 mg/kg body weight per day, preferably between 0.5 and about 75 mg/kg body weight per day and most preferably between about 1 and 50 mg/kg body weight per day of the active ingredient compound are useful in a monotherapy 10 for the prevention and treatment of IL-1-, apoptosis-, IGIF-, and IFN- $\gamma$ -mediated diseases; including inflammatory diseases, autoimmune diseases, destructive bone disorders, proliferative disorders, infectious diseases, 15 degenerative diseases, necrotic diseases, inflammatory peritonitis, osteoarthritis, acute pancreatitis, chronic pancreatitis, asthma, adult respiratory distress syndrome, glomerulonephritis, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Graves' disease, autoimmune gastritis, insulin-dependent diabetes mellitus (Type I), autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, chronic active hepatitis, myasthenia 20 gravis, inflammatory bowel disease, Crohn's disease, psoriasis, graft vs. host disease, osteoporosis, multiple 25 myeloma-related bone disorder, acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, multiple myeloma, sepsis, septic shock, Shigellosis, Alzheimer's disease, Parkinson's disease, cerebral ischemia, myocardial 30 ischemia, spinal muscular atrophy, multiple sclerosis, AIDS-related encephalitis, HIV-related encephalitis, aging, alopecia, neurological damage due to stroke, ulcerative colitis, traumatic brain injury, organ 35 transplant rejection, infectious hepatitis, juvenile

diabetes, lichenplanus, acute dermatomyositis, eczema, primary cirrhosis, uveitis, Behcet's disease, atopic skin disease, pure red cell aplasia, aplastic anemia, amyotrophic lateral sclerosis, nephrotic syndrome and  
5 systemic diseases or diseases with effects localized in the liver or other organs having an inflammatory or apoptotic component caused by excess dietary alcohol intake or viruses, such as HBV, HCV, HGV, yellow fever virus, dengue fever virus, and Japanese encephalitis  
10 virus.

Typically, the pharmaceutical compositions of this invention will be administered from about 1 to 5 times per day or alternatively, as a continuous infusion. Such administration can be used as a chronic or acute  
15 therapy. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. A typical preparation will contain from about 5% to about 95%  
20 active compound (w/w). Preferably, such preparations contain from about 20% to about 80% active compound.

When the compositions of this invention comprise a combination of a compound of formulae (I) or (II) and one or more additional therapeutic or prophylactic agents, both the compound and the additional agent should be present at dosage levels of between about  
25 10% to 80% of the dosage normally administered in a monotherapy regime.

Upon improvement of a patient's condition, a  
30 maintenance dose of a compound, composition or combination of this invention may be administered, if necessary. Subsequently, the dosage or frequency of administration, or both, may be reduced, as a function of the symptoms, to a level at which the improved condition  
35 is retained when the symptoms have been alleviated to the

desired level, treatment should cease. Patients may, however, require intermittent treatment on a long-term basis upon any recurrence or disease symptoms.

As the skilled artisan will appreciate, lower 5 or higher doses than those recited above may be required. Specific dosage and treatment regimens for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health status, sex, diet, time of 10 administration, rate of excretion, drug combination, the severity and course of the disease, and the patient's disposition to the disease and the judgment of the treating physician.

IL-1 or apoptosis mediated diseases may be 15 treated or prevented by the compounds of this invention. Such diseases include, but are not limited to, inflammatory diseases, autoimmune diseases, destructive bone disorders, proliferative disorders, infectious diseases, and degenerative diseases.

The IL-1 or apoptosis mediated inflammatory 20 diseases which may be treated or prevented include, but are not limited to osteoarthritis, acute pancreatitis, chronic pancreatitis, asthma, inflammatory peritonitis, and adult respiratory distress syndrome. Preferably the 25 inflammatory disease is osteoarthritis or acute pancreatitis.

The IL-1 or apoptosis mediated autoimmune 30 diseases which may be treated or prevented include, but are not limited to, glomerulonephritis, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Graves' disease, autoimmune gastritis, insulin-dependent diabetes mellitus (Type I), autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, chronic active hepatitis, myasthenia 35 gravis, multiple sclerosis, inflammatory bowel disease,

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Crohn's disease, psoriasis, and graft vs. host disease. Preferably the autoimmune disease is rheumatoid arthritis, inflammatory bowel disease, Crohn's disease, or psoriasis.

5 IL-1 or apoptosis mediated destructive bone disorders which may be treated or prevented include, but are not limited to, osteoporosis and multiple myeloma-related bone disorder.

10 The IL-1 or apoptosis mediated proliferative diseases which may be treated or prevented include, but are not limited to, acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, and multiple myeloma.

15 The IL-1 or apoptosis mediated infectious diseases which may be treated or prevented include, but are not limited to, sepsis, septic shock, and Shigellosis.

20 The IL-1 or apoptosis mediated degenerative or necrotic diseases which may be treated or prevented by the compounds of this invention include, but are not limited to, Alzheimer's disease, Parkinson's disease, cerebral ischemia, and myocardial ischemia. Preferably, the degenerative disease is Alzheimer's disease.

25 The IL-1 or apoptosis mediated degenerative diseases which may be treated or prevented by the compounds of this invention include, but are not limited to, Alzheimer's disease, Parkinson's disease, cerebral ischemia, myocardial ischemia, spinal muscular atrophy, multiple sclerosis, AIDS-related encephalitis, HIV-related encephalitis, aging, alopecia, and neurological damage due to stroke.

30 Other diseases having an inflammatory or apoptotic component may be treated or prevented by the compounds of this invention. Such diseases may be 35 systemic diseases or diseases with effects localized in

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the liver or other organs and may be caused by, for example, excess dietary alcohol intake or viruses, such as HBV, HCV, HGV, yellow fever virus, dengue fever virus, and Japanese encephalitis virus.

5           IGIF- or IFN- $\gamma$ -mediated diseases may also be treated or prevented by the compounds of this invention. Such diseases include, but are not limited to, inflammatory, infectious, autoimmune, proliferative, neurodegenerative and necrotic conditions.

10          The IGIF- or IFN- $\gamma$ -mediated inflammatory diseases which may be treated or prevented include, but are not limited to osteoarthritis, acute pancreatitis, chronic pancreatitis, asthma, rheumatoid arthritis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, 15 cerebral ischemia, myocardial ischemia and adult respiratory distress syndrome. Preferably, the inflammatory disease is rheumatoid arthritis, ulcerative colitis, Crohn's disease, hepatitis or adult respiratory distress syndrome.

20          The IGIF- or IFN- $\gamma$ -mediated infectious diseases which may be treated or prevented include, but are not limited to infectious hepatitis, sepsis, septic shock and Shigellosis.

25          The IGIF- or IFN- $\gamma$ -mediated autoimmune diseases which may be treated or prevented include, but are not limited to glomerulonephritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Graves' disease, autoimmune gastritis, insulin-dependent diabetes mellitus (Type I), juvenile diabetes, autoimmune 30 hemolytic anemia, autoimmune neutropenia, thrombocytopenia, myasthenia gravis, multiple sclerosis, psoriasis, lichenplanus, graft vs. host disease, acute dermatomyositis, eczema, primary cirrhosis, hepatitis, uveitis, Behcet's disease, atopic skin disease, pure red 35 cell aplasia, aplastic anemia, amyotrophic lateral

sclerosis and nephrotic syndrome. Preferably, the autoimmune disease is glomerulonephritis, insulin-dependent diabetes mellitus (Type I), juvenile diabetes, psoriasis, graft vs. host disease, or hepatitis.

5 More preferred diseases which may be treated or prevented by the compounds of this invention include rheumatoid arthritis, inflammatory bowel disease, including Crohn's disease and ulcerative colitis, inflammatory peritonitis, septic shock, pancreatitis, 10 traumatic brain injury, organ transplant rejection, osteoarthritis, and asthma.

Accordingly, one embodiment of this invention provides a method for treating or preventing an IL-1 or apoptosis mediated disease in a subject comprising the 15 step of administering to the subject any compound, pharmaceutical composition, or combination described herein and a pharmaceutically acceptable carrier.

Another embodiment of this invention provides a method for decreasing IGIF production in a subject comprising the step of administering to the subject any 20 compound, pharmaceutical composition, or combination described herein and a pharmaceutically acceptable carrier.

Another embodiment of this invention provides a 25 method for decreasing IFN- $\gamma$  production in a subject comprising the step of administering to the subject any compound, pharmaceutical composition, or combination described herein and a pharmaceutically acceptable carrier.

30 Although this invention focuses on the use of the compounds disclosed herein for preventing and treating IL-1, apoptosis-, IGIF, and IFN- $\gamma$ -mediated diseases, the compounds of this invention can also be used as inhibitory agents for other cysteine proteases.

The compounds of this invention are also useful as commercial reagents which effectively bind to caspases or other cysteine proteases including, but not limited to ICE. As commercial reagents, the compounds of this 5 invention, and their derivatives, may be used to block proteolysis of a target peptide in biochemical or cellular assays for ICE and ICE homologs or may be derivatized to bind to a stable resin as a tethered substrate for affinity chromatography applications.

10 These and other uses which characterize commercial cysteine protease inhibitors will be evident to those of ordinary skill in the art.

In order that this invention be more fully understood, the following examples are set forth. These 15 examples are for the purpose of illustration only and are not to be construed as limiting the scope of the invention in any way.

#### General Methods

20 The compounds of this invention may be evaluated in various biological assays, including those described in Examples 2-4.

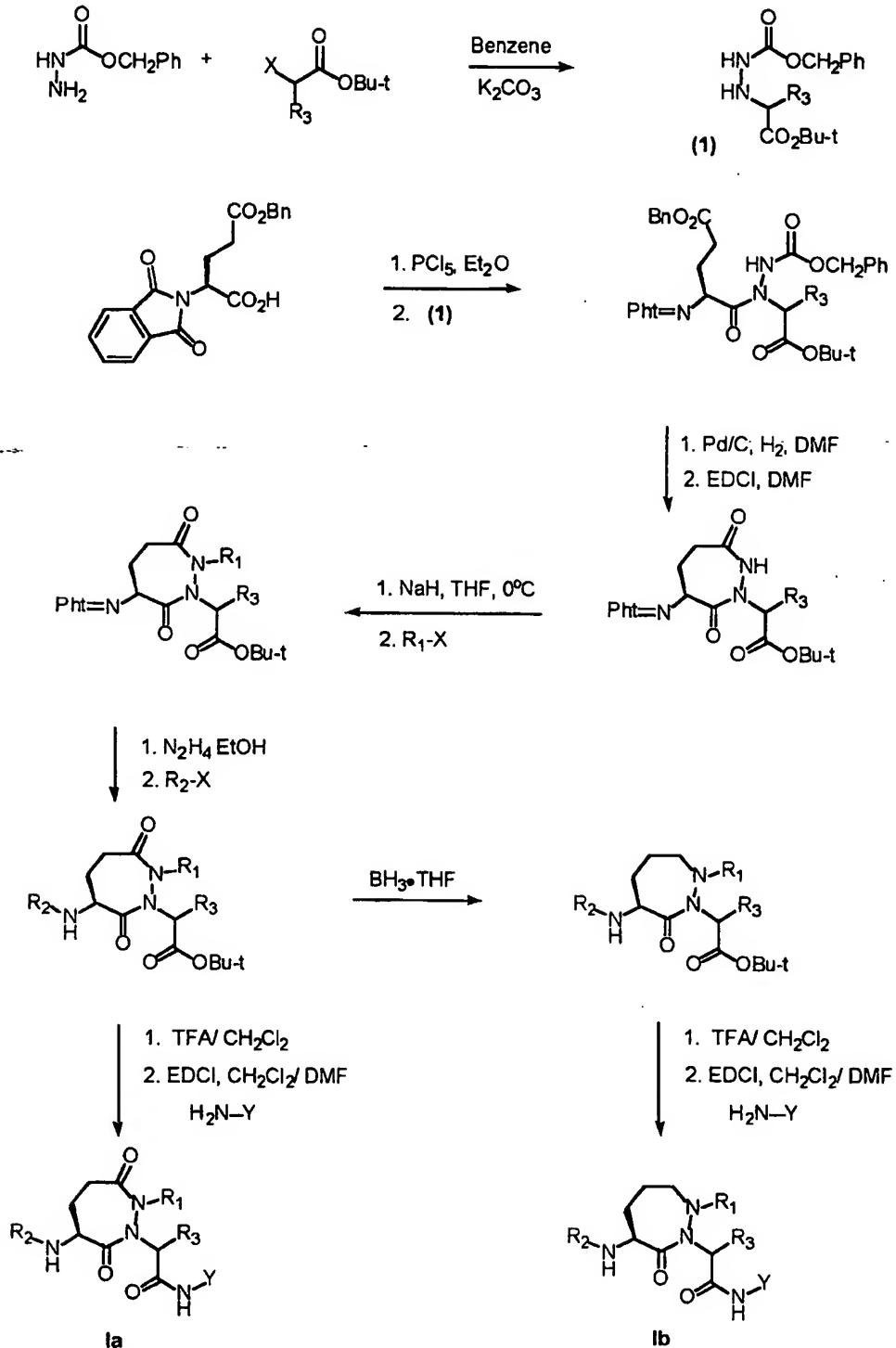
Other assays that may be used to evaluate the 25 compounds of this invention are disclosed in PCT application PCT/US96/20843, published June 26, 1997, under publication no. WO 97/22619, which is incorporated herein by reference. Such assays include in vivo bioavailability determinations, pharmacokinetic studies in the mouse, inhibition of ICE homologs, inhibition of apoptosis, in vivo acute assay for anti-inflammatory efficacy, measurement of blood levels, IGF assays, mouse carageenan peritoneal inflammation assay, and type II collagen-induced arthritis.

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Example 1

- Compounds of this invention may be prepared according to published procedures, such as the procedures described in Robl, J.A. et al., Bioorg. Med. Chem. Lett. 5 4, pp. 2055-2060 (1994) or United States Patent No. 4,465,679, which are incorporated herein by reference. Skilled practitioners will realize that such procedures may be modified to obtain the compounds of this invention.
- 10 For example, compounds represented by formulae (Ia) or (Ib) may be prepared as described in Scheme 1.

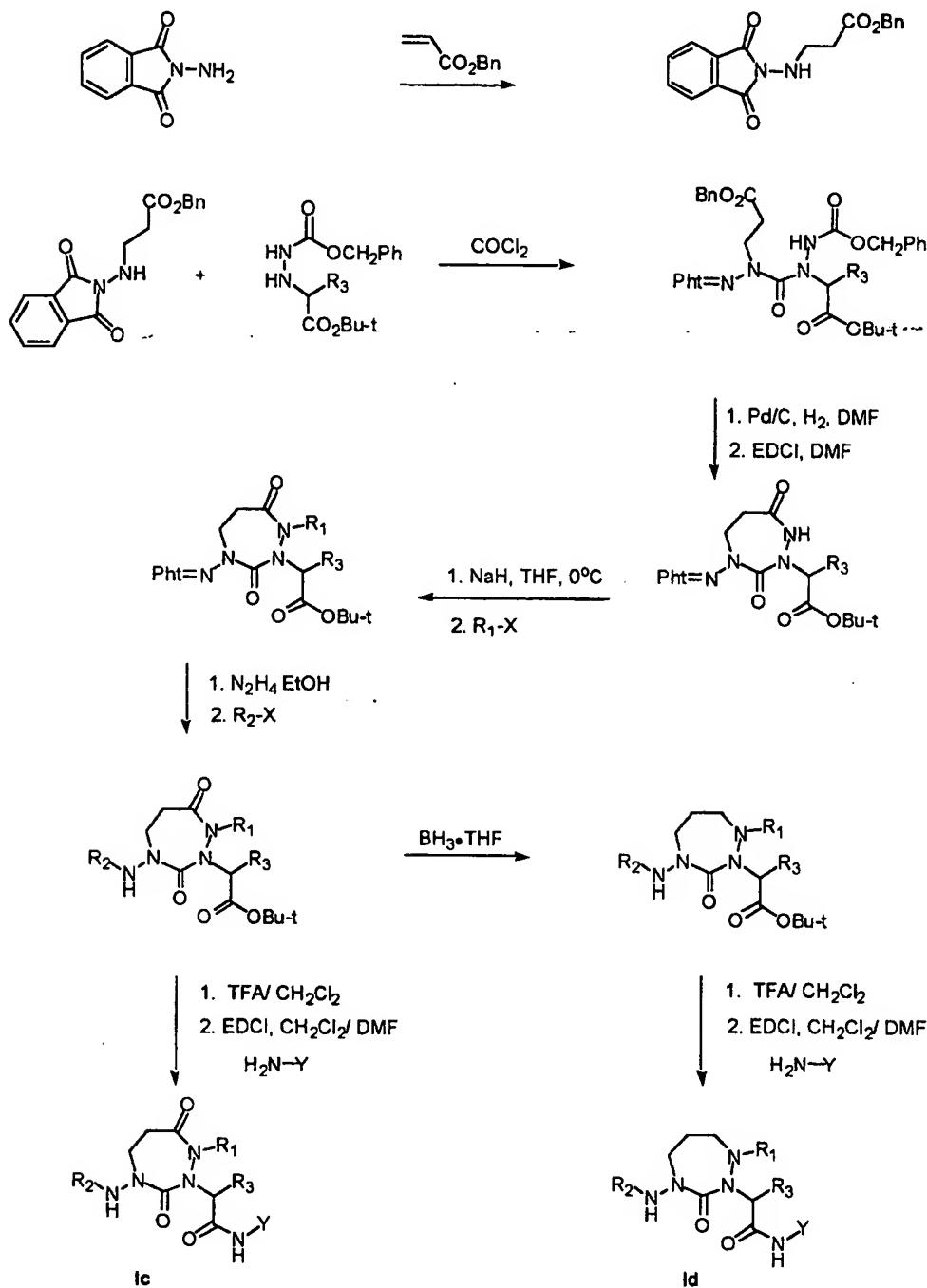
Scheme 1. Synthesis of analogs of Embodiment Ia and Ib



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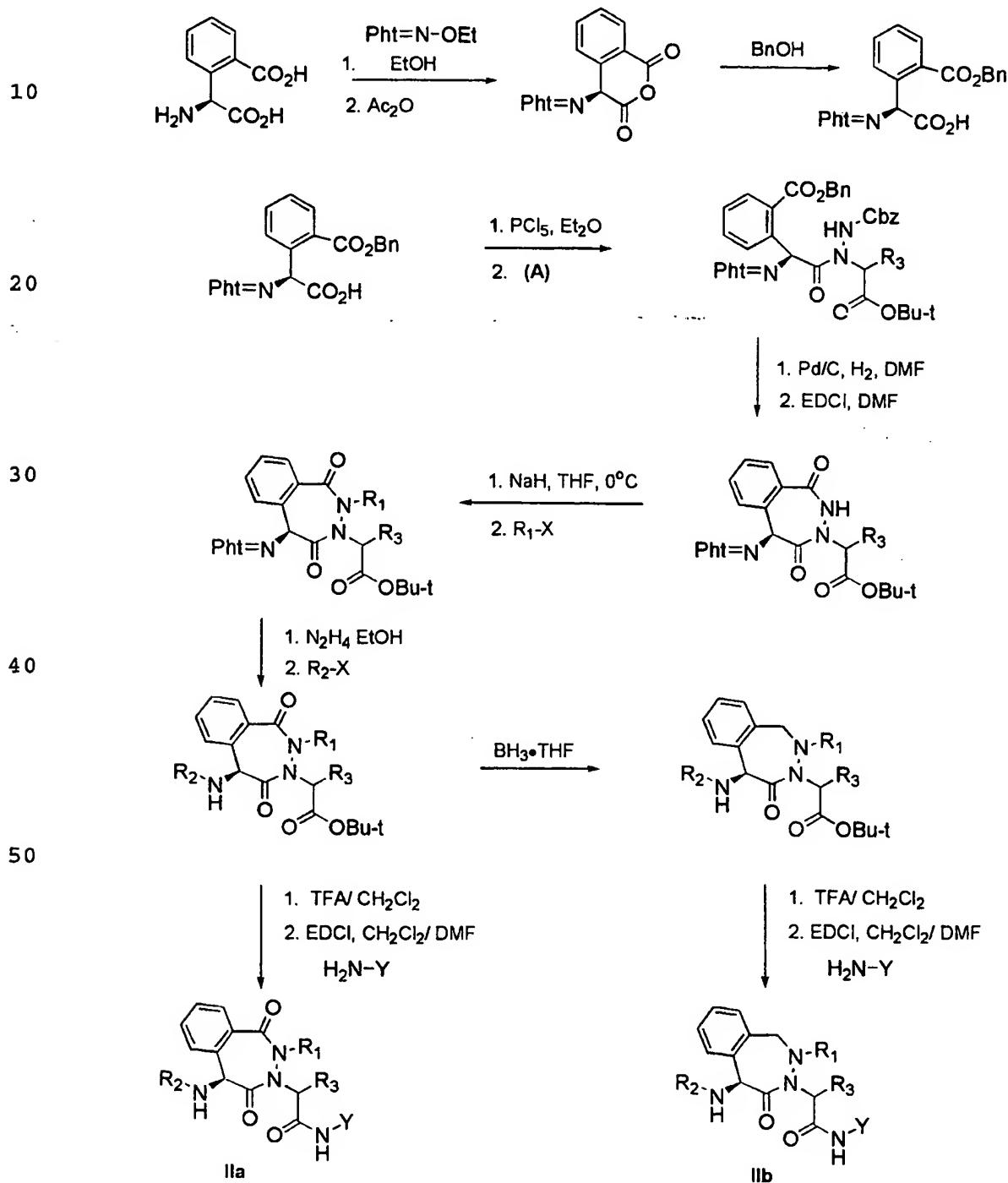
For example, compounds represented by formulae (Ic) or (Id) may be prepared as described in Scheme 2.

Scheme 2. Synthesis of analogs of Embodiment Ic and Id



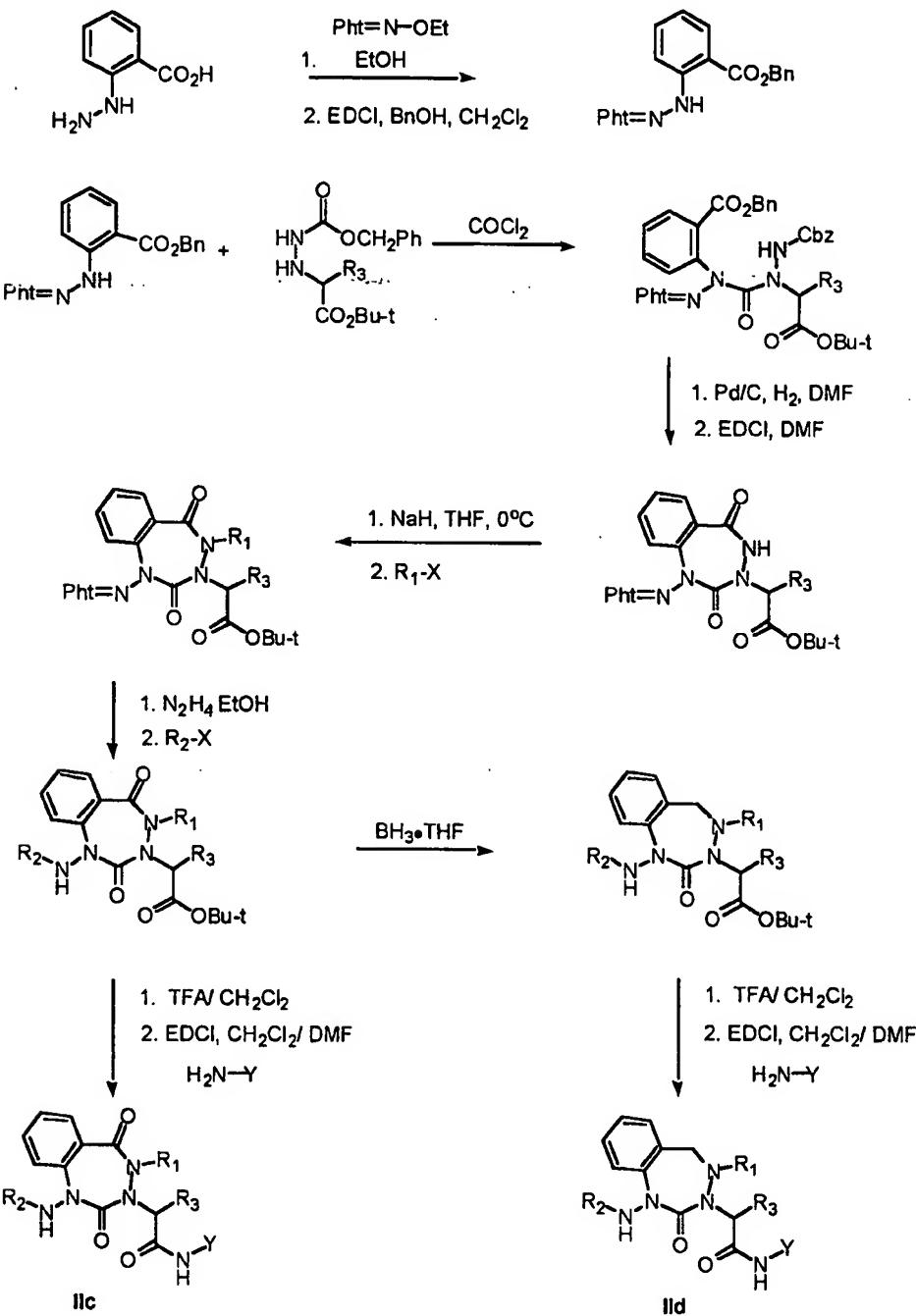
For example, compounds represented by formulae (IIa) or (IIb) may be prepared as described in Scheme 3.

Scheme 3. Synthesis of Embodiments IIa and IIb



For example, compounds represented by formulae (IIc) or (IId) may be prepared as described in Scheme 4:

Scheme 4. Synthesis of Embodiments IIc and IId

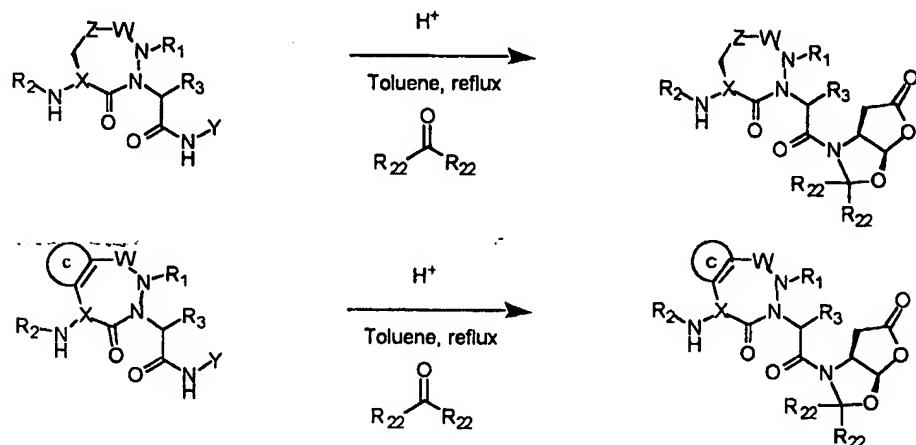


Compounds represented by formulae (I) or (II), wherein R<sup>19</sup> and Y, together with the nitrogen atom to which they are bound, form a ring (g), may be prepared as described in Scheme 5.

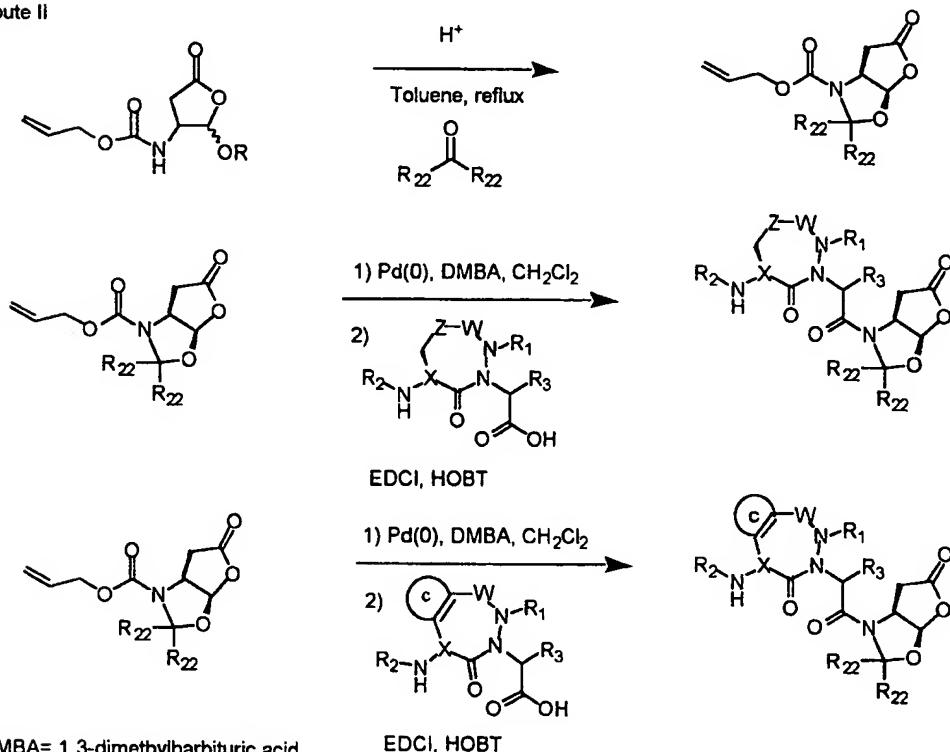
5

Scheme 5. Synthesis of analogs of Embodiment (g)

Route I



Route II



DMBA= 1,3-dimethylbarbituric acid

Scheme 5 describes the synthesis of compounds wherein m is 0. Compounds wherein m is 1 may be prepared by similar methods. The Nalloc protected amine may be protected with other groups that are well known to the skilled practitioner. The palladium coupling method is described in more detail in PCT application PCT/US96/20843, publication no. WO 97/22619, which is incorporated herein by reference.

Schemes 1-5 describes the synthesis of certain embodiments of this invention. Other embodiments may be prepared by similar methods.

#### Example 2

##### 1. Enzyme assay with UV-visible substrate

This assay is run using an Succinyl-Tyr-Val-Ala-Asp-p-Nitroanilide substrate. Synthesis of analogous substrates is described by L.A. Reiter (Int. J. Peptide Protein Res., 43, pp. 87-96 (1994)). The assay mixture contains:

65  $\mu$ l buffer (10mM Tris, 1 mM DTT, 0.1% CHAPS @pH 8.1)  
10  $\mu$ l ICE (50 nM final concentration to give a rate of ~1mOD/min)  
5  $\mu$ l DMSO/Inhibitor mixture  
20  $\mu$ l 400 $\mu$ M Substrate (80  $\mu$ M final concentration)  
100 $\mu$ l total reaction volume

The visible ICE assay is run in a 96-well microtiter plate. Buffer, ICE and DMSO (if inhibitor is present) are added to the wells in the order listed. The components are left to incubate at room temperature for 15 minutes starting at the time that all components are present in all wells. The microtiter plate reader is set to incubate at 37 °C. After the 15 minute incubation, substrate is added directly to the wells and the reaction is monitored by following the release of the chromophore

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(pNA) at 405 - 603 nm at 37 °C for 20 minutes. A linear fit of the data is performed and the rate is calculated in mOD/min. DMSO is only present during experiments involving inhibitors, buffer is used to make up the 5 volume to 100 µl in the other experiments.

## 2. Enzyme Assay with Fluorescent Substrate

This assay is run essentially according to Thornberry et al., Nature, 356 pp. 768-774 (1992), using substrate 17 referenced in that article. The substrate is: Acetyl-Tyr-Val-Ala-Asp-amino-4-methylcoumarin (AMC). The following components are mixed:

15      65 µl buffer(10mM Tris, 1mM DTT, 0.1% CHAPS @pH8.1)  
10 µl ICE (2 - 10 nM final concentration)  
5 µl DMSO/inhibitor solution  
20 µl 150 µM Substrate (30 µM final)  
100µl total reaction volume

20      The assay is run in a 96-well microtiter plate. Buffer and ICE are added to the wells. The components are left to incubate at 37 °C for 15 minutes in a temperature-controlled wellplate. After the 15 minute incubation, the reaction is started by adding substrate 25 directly to the wells and the reaction is monitored at 37 °C for 30 minutes by following the release of the AMC fluorophore using an excitation wavelength for 380 nm and an emission wavelength of 460 nm. A linear fit of the data for each well is performed and a rate is determined 30 in fluorescence units per second.

35      For determination of enzyme inhibition constants ( $K_i$ ) or the mode of inhibition (competitive, uncompetitive or noncompetitive), the rate data determined in the enzyme assays at varying inhibitor concentrations are computer-fit to standard enzyme

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kinetic equations (see I.H. Segel, Enzyme Kinetics, Wiley-Interscience, 1975).

The determination of second order rate constants for irreversible inhibitors was performed by fitting the fluorescence vs time data to the progress equations of Morrison. Morrison, J.F., Mol. Cell. Biophys., 2, pp. 347-368 (1985). Thornberry et al. published a description of these methods for measurement of rate constants of irreversible inhibitors of ICE.

Thornberry, N.A., et al. Biochemistry, 33, pp. 3923-3940 (1994). For compounds where no prior complex formation can be observed kinetically, the second order rate constants ( $k_{inact}$ ) are derived directly from the slope of the linear plots of  $k_{obs}$  vs. inhibitor concentration [I].

For compounds where prior complex formation to the enzyme can be detected, the hyperbolic plots of  $k_{obs}$  vs. [I] are fit to the equation for saturation kinetics to first generate  $K_i$  and  $k'$ . The second order rate constant  $k_{inact}$  is then given by  $k'/K_i$ .

20

3. PBMC Cell assay

IL-1 $\beta$  Assay with a Mixed Population of Human Peripheral Blood Mononuclear Cells (PBMC) or Enriched Adherent Mononuclear Cells

25

Processing of pre-IL-1 $\beta$  by ICE can be measured in cell culture using a variety of cell sources. Human PBMC obtained from healthy donors provides a mixed population of lymphocyte subtypes and mononuclear cells that produce a spectrum of interleukins and cytokines in response to many classes of physiological stimulators. Adherent mononuclear cells from PBMC provides an enriched source of normal monocytes for selective studies of cytokine production by activated cells.

35

**Experimental Procedure:**

An initial dilution series of test compound in DMSO or ethanol is prepared, with a subsequent dilution into RPMI-10% FBS media (containing 2 mM L-glutamine, 10 mM HEPES, 50 U and 50 ug/ml pen/strep) respectively to yield drugs at 4x the final test concentration containing 0.4% DMSO or 0.4% ethanol. The final concentration of DMSO is 0.1% for all drug dilutions. A concentration titration which brackets the apparent  $K_i$  for a test compound determined in an ICE inhibition assay is generally used for the primary compound screen.

Generally 5-6 compound dilutions are tested and the cellular component of the assay is performed in duplicate, with duplicate ELISA determinations on each cell culture supernatant.

**PBMC Isolation and IL-1 Assay:**

Buffy coat cells isolated from one pint human blood (yielding 40-45 ml final volume plasma plus cells) are diluted with media to 80 ml and LeukoPREP separation tubes (Becton Dickinson) are each overlaid with 10 ml of cell suspension. After 15 min centrifugation at 1500-1800 xg, the plasma/media layer is aspirated and then the mononuclear cell layer is collected with a Pasteur pipette and transferred to a 15 ml conical centrifuge tube (Corning). Media is added to bring the volume to 15 ml, gently mix the cells by inversion and centrifuge at 300 xg for 15 min. The PBMC pellet is resuspended in a small volume of media, the cells are counted and adjusted to  $6 \times 10^6$  cells/ml.

For the cellular assay, 1.0 ml of the cell suspension is added to each well of a 24-well flat bottom tissue culture plate (Corning), 0.5 ml test compound dilution and 0.5 ml LPS solution (Sigma #L-3012; 20 ng/ml solution prepared in complete RPMI media; final LPS

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concentration 5 ng/ml). The 0.5 ml additions of test compound and LPS are usually sufficient to mix the contents of the wells. Three control mixtures are run per experiment, with either LPS alone, solvent vehicle 5 control, and/or additional media to adjust the final culture volume to 2.0 ml. The cell cultures are incubated for 16-18 hr at 37 °C in the presence of 5% CO<sub>2</sub>.

At the end of the incubation period, cells are 10 harvested and transferred to 15 ml conical centrifuge tubes. After centrifugation for 10 min at 200 xg, supernatants are harvested and transferred to 1.5 ml Eppendorf tubes. It may be noted that the cell pellet may be utilized for a biochemical evaluation of pre-IL-1 $\beta$  15 and/or mature IL-1 $\beta$  content in cytosol extracts by Western blotting or ELISA with pre-IL-1 $\beta$  specific antisera.

Isolation of Adherent Mononuclear cells:

PBMC are isolated and prepared as described above. Media (1.0 ml) is first added to wells followed by 0.5 ml of the PBMC suspension. After a one hour 20 incubation, plates are gently shaken and nonadherent cells aspirated from each well. Wells are then gently washed three times with 1.0 ml of media and final 25 resuspended in 1.0 ml media. The enrichment for adherent cells generally yields  $2.5-3.0 \times 10^5$  cells per well. The addition of test compounds, LPS, cell incubation conditions and processing of supernatants proceeds as 30 described above.

ELISA:

Quantikine kits (R&D Systems) may be used for the measurement of mature IL-1 $\beta$ . Assays are performed 35 according to the manufacturer's directions. Mature IL-1 $\beta$

levels of about 1-3 ng/ml in both PBMC and adherent mononuclear cell positive controls are observed. ELISA assays are performed on 1:5, 1:10 and 1:20 dilutions of supernatants from LPS-positive controls to select the 5 optimal dilution for supernatants in the test panel.

The inhibitory potency of the compounds can be represented by an IC<sub>50</sub> value, which is the concentration of inhibitor at which 50% of mature IL-1 $\beta$  is detected in the supernatant as compared to the positive controls.

10 The skilled practitioner realizes that values obtained in cell assays may depend on multiple factors. The values may not necessarily represent fine quantitative results.

15 Example 3

Whole Blood Assay for IL-1 $\beta$  Production

Whole blood assay IC<sub>50</sub> values for compounds of this invention were obtained using the method described below:

20 Purpose:  
The whole blood assay is a simple method for measuring the production of IL-1 $\beta$  (or other cytokines) and the activity of potential inhibitors. The complexity 25 of this assay system, with its full complement of lymphoid and inflammatory cell types, spectrum of plasma proteins and red blood cells is an ideal in vitro representation of human in vivo physiologic conditions.

30 Materials:

Pyrogen-free syringes (~ 30 cc)

Pyrogen-free sterile vacuum tubes containing lyophilized Na<sub>2</sub>EDTA (4.5 mg/10 ml tube)

Human whole blood sample (~ 30-50 cc)

35 1.5 ml Eppendorf tubes

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- Test compound stock solutions (~ 25mM in DMSO or other solvent)  
Endotoxin-free sodium chloride solution (0.9%) and HBSS  
Lipopolysaccharide (Sigma; Cat.# L-3012) stock solution  
5 at 1mg/ml in HBSS  
IL-1 $\beta$  ELISA Kit (R & D Systems; Cat # DLB50)  
TNF $\alpha$  ELISA Kit (R & D Systems; Cat # DTA50)  
Water bath or incubator

10 Whole Blood Assay Experimental Procedure:

Set incubator or water bath at 30 °C. Aliquot 0.25 ml of blood into 1.5 ml Eppendorf tubes. Note: be sure to invert the whole blood sample tubes after every two aliquots. Differences in replicates may result if 15 the cells sediment and are not uniformly suspended. Use of a positive displacement pipette will also minimize differences between replicate aliquots.

Prepare drug dilutions in sterile pyrogen-free saline by serial dilution. A dilution series which 20 brackets the apparent  $K_i$  for a test compound determined in an ICE inhibition assay is generally used for the primary compound screen. For extremely hydrophobic compounds, prepare compound dilutions in fresh plasma obtained from the same blood donor or in PBS-containing 25 5% DMSO to enhance solubility.

Add 25  $\mu$ l test compound dilution or vehicle control and gently mix the sample. Then add 5.0  $\mu$ l LPS solution (250 ng/ml stocked prepared fresh: 5.0 ng/ml final concentration LPS), and mix again. Incubate the 30 tubes at 30 °C in a water bath for 16-18 hr with occasional mixing. Alternatively, the tubes can be placed in a rotator set at 4 rpm for the same incubation period. This assay should be set up in duplicate or triplicate with the following controls: negative control 35 - no LPS; positive control - no test inhibitor; vehicle

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control - the highest concentration of DMSO or compound solvent used in the experiment. Additional saline is added to all control tubes to normalize volumes for both control and experimental whole blood test samples.

- 5        After the incubation period, whole blood samples are centrifuged for 10 minutes at ~ 2000 rpm in the microfuge, plasma is transferred to a fresh microfuge tube and centrifuged at 1000 x g to pellet residual platelets if necessary. Plasma samples may be stored  
10      frozen at -70 °C prior to assay for cytokine levels by ELISA.

ELISA:

- R & D Systems (614 McKinley Place N.E.  
15      Minneapolis, MN 55413) Quantikine kits may be used for measurement of IL-1 $\beta$  and TNF- $\alpha$ . The assays are performed according to the manufacturer's directions. IL-1 $\beta$  levels of ~ 1-5 ng/ml in positive controls among a range of individuals may be observed. A 1:200 dilution of plasma  
20      for all samples is usually sufficient for experiments for ELISA results to fall on the linear range of the ELISA standard curves. It may be necessary to optimize standard dilutions if you observe differences in the whole blood assay. Nerad, J.L. et al., J. Leukocyte Biol., 52, pp. 687-692 (1992).

Example 4

- The antiviral efficacy of compounds may be evaluated in various in vitro and in vivo assays. For  
30      example, compounds may be tested in in vitro viral replication assays. In vitro assays may employ whole cells or isolated cellular components. In vivo assays include animal models for viral diseases. Examples of such animal models include, but are not limited to,  
35      rodent models for HBV or HCV infection, the Woodchuck

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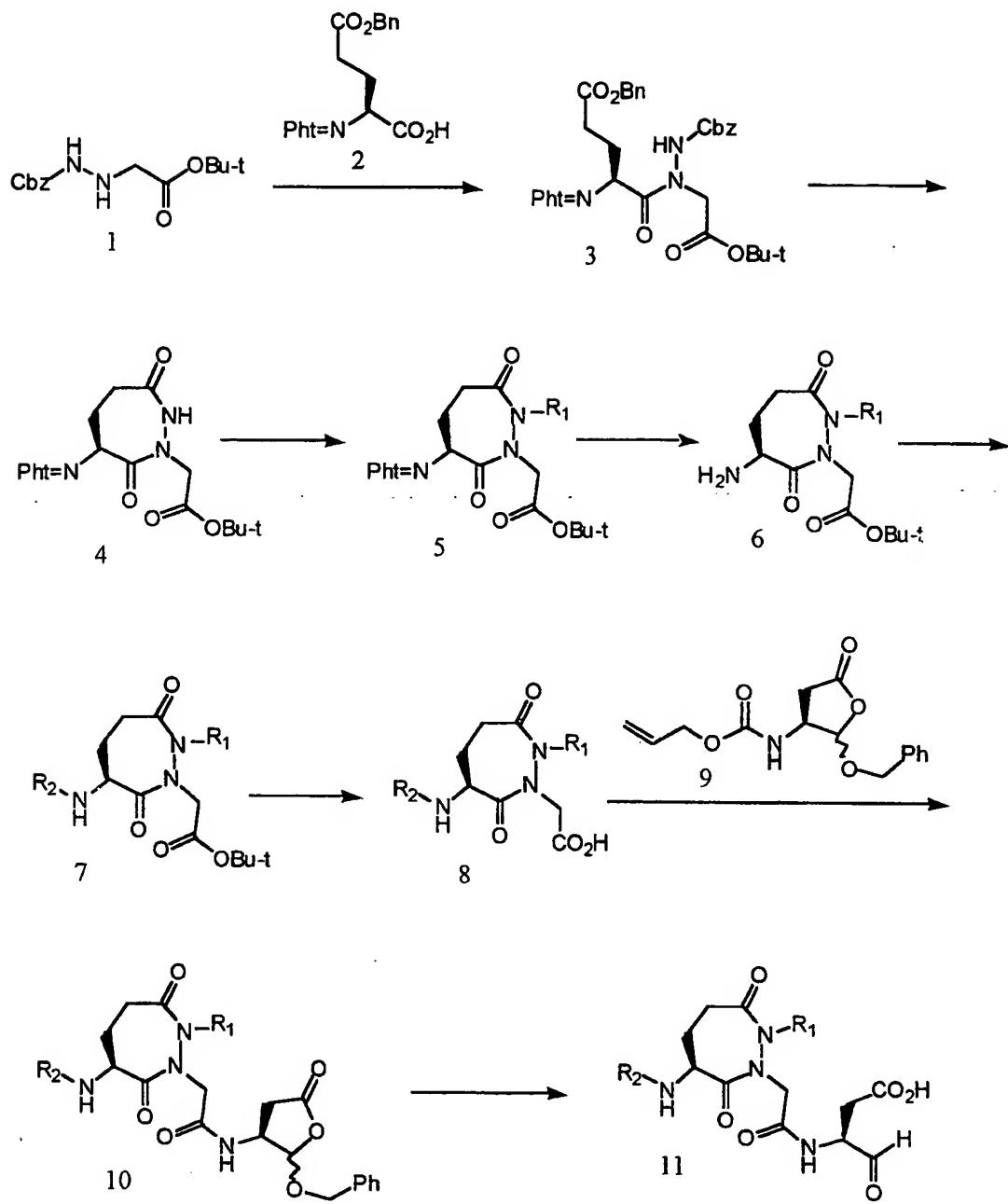
model for HBV infection, and chimpanzee model for HCV infection.

Compounds of this invention may also be evaluated in animal models for dietary alcohol-induced  
5 disease.

Example 5

Compounds 10a - 10d and 11a - 11d were prepared as described below:

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Compounds	R <sub>1</sub>
5a and 6a	Benzyl
5b	Allyl
5c and 6c	1-Propyl

Compounds	R <sub>1</sub>	R <sub>2</sub>
7b 8b 10b 11b	1-Propyl	
7c 8c 10c	1-Propyl	
10d 11c	1-Propyl	

**Preparation of (N-Benzylloxycarbonyl-hydrazino)-acetic acid tert-butyl ester (1).** To a mixture of benzyl carbamate (25.0 g, 150 mmol), potassium carbonate (20.78 g, 150 mmol) in 230 mL of dimethylformamide (DMF) was added tert-butyl bromoacetate (26.4 g, 145 mmol). The suspension was stirred at room temperature for 16 hours. The reaction mixture was diluted with 1000 mL of ethyl acetate, washed with ice water then water three times. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated *in vacuo* to afford a clear oil, which was purified by flash chromatography using hexane/EtOAc (9/1 to 7/3) to give 23.55 g (62% yield) of the title compound. <sup>1</sup>H-NMR (500MHz, CDCl<sub>3</sub>) δ 1.45 (s, 9H), 3.55 (s, 2H), 4.20 (br, 1H), 5.15 (s, 2H), 6.70 (br, 1H), 7.40 (s, 5H). Analytical HPLC\*: 10.11 min.

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**Preparation of 2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-pentanedioic acid 5-benzyl ester (2).** A mixture of  $\gamma$ -benzyl-1-glutamate (11.85 g, 50 mmol) and phthalic anhydride (7.40 g, 50 mmol) in toluene (150 mL) was refluxed with a Dean-Stark tube for 16 hours. Solvent was removed under reduced pressure. The residue was purified by flash chromatography using hexane/ethyl acetate/acetic acid (90/10/1 to 50/50/1) to afford 14.83 g (80% yield) of the title compound.  $^1\text{H-NMR}$  (500MHz,  $\text{CDCl}_3$ )  $\delta$  2.40-2.70 (m, 4H), 4.95-5.10 (m, 3H), 7.27-7.40 (m, 5H), 7.70-7.95 (m, 4H). Analytical HPLC: 13.28 min. LC-MS (ES $^+$ ): m/e = 368 ( $\text{M}+\text{H}^+$ ) ..

**Preparation of 5-(N'-Benzylloxycarbonyl-N-tert-butoxycarbonylmethyl-hydrazino)-4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-5-oxo-pentanoic acid benzyl ester (3).** To a solution of 2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-pentanedioic acid 5-benzyl ester (2) (1.84 g, 5 mmol) in 25 mL of dichloromethane with 0.1 mL of dimethylformamide (DMF) was dropwise added oxalyl chloride (666 mg, 5.25 mmol) at 0°C. The solution was stirred at 0°C for 30 min then at room temperature for one hour.  $\text{K}_2\text{CO}_3$  (1.03 g) was added at 0°C followed by a solution of (N-benzylloxycarbonyl-hydrazino)-acetic acid tert-butyl ester (1) (1.40 g, 5 mmol) in 5 ml of dichloromethane. The mixture was stirred at room temperature for 16 hours. The solvent was removed under reduced pressure and the residue was suspended in 400 mL of ethyl acetate, washed with water (200 mL x 2) then brine (200 mL x 2). The organic layer was dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered, concentrated *in vacuo* to afford 2.8 g of clear oil. Flash chromatography using hexane/ethyl acetate (9/1 to 7/3) gave 1.93 g (61% yield) of the title compound.  $^1\text{H-NMR}$  (500MHz,  $\text{CDCl}_3$ )  $\delta$  1.35 (s, 9H), 2.30-2.55 (m, 4H), 4.70-5.20 (br, 4H), 5.08 (s, 2H), 5.30 (m, 1H), 7.26-7.35

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(m, 10H), 7.65-7.90 (m, 4H). Analytical HPLC: 14.6 min.  
LC-MS (ES<sup>+</sup>): m/e = 630 (M+H<sup>+</sup>).

**Preparation of [6-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-3,7-dioxo-[1,2]diazepan-1-yl]-acetic acid tert-butyl ester (4).** A suspension of 5-(N'-benzyloxycarbonyl-N-tert-butoxycarbonylmethyl-hydrazino)-4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-5-oxo-pentanoic acid benzyl ester (3) and 10% palladium on carbon (250 mg) in tetrahydrofuran (THF) (30 mL) and DMF (3mL) was stirred under hydrogen atmosphere for 16 hours. The mixture was filtered through Celite and the filtrate was evaporated in vacuo. The residue was dissolved in 30 mL of dichloromethane. 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) (770 mg, 4 mmol) was added and the solution was stirred at room temperature for 3.5 hours. Solvent was removed in vacuo and the residue was dissolved in ethyl acetate (300 mL), then washed with water (100 mL x 2). The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, purified by flash chromatography using hexane/ethyl acetate (85/15 to 50/50) to afford 1.06 g (75% yield) of the title compound. <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ 1.40 (s, 9H), 2.30-2.40 (m, 1H), 2.40-2.50 (m, 1H), 3.05-3.12 (m, 1H), 3.38-3.48 (m, 1H), 3.90-4.00 (d, 1H), 4.60-4.70 (d, 1H), 5.55-5.63 (m, 1H), 7.65 (s, 1H), 7.75-7.7.9 (m, 2H), 7.88-7.92 (m, 2H). Analytical HPLC: 10.36 min. LC-MS (ES<sup>+</sup>): m/e = 388 (M+H<sup>+</sup>).

**Preparation of [2-Benzyl-6-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-3,7-dioxo-[1,2]diazepan-1-yl]-acetic acid tert-butyl ester (5a).** A mixture of [6-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-3,7-dioxo-[1,2]diazepan-1-yl]-acetic acid tert-butyl ester (4) (200 mg, 0.52 mmol), benzyl bromide (110 mg, 0.64 mmol), K<sub>2</sub>CO<sub>3</sub> (125 mg, 0.9

mmol) and benzyltriethylammonium chloride (15 mg) in THF (5 mL) was stirred at room temperature for 40 hours. The mixture was diluted with ethyl acetate (100 mL) and washed with water three times. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub> and filtered. The filtrate was purified by flash chromatography using dichloromethane/ethyl acetate (99.5/0.5 to 97.5/2.5) to afford 166 mg (67% yield) of the title compound. <sup>1</sup>H-NMR (500MHz, CDCl<sub>3</sub>) δ 1.40 (s, 9H), 2.30-2.40 (m, 1H), 2.50-2.57 (m, 1H), 3.30-3.40 (m, 1H), 3.60-3.68 (m, 1H), 3.72-3.80 (d, 1H), 4.48-4.52 (d, 1H), 4.80-4.92 (q, 2H), 5.15-5.20 (m, 1H), 7.35 (s, 5H), 7.70 (d, 2H), 7.82 (d, 2H). Analytical HPLC: 13.43 min. LC-MS (ES<sup>+</sup>): m/e = 478 (M+H<sup>+</sup>).

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[2-Allyl-6-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-3,7-dioxo-[1,2]diazepan-1-yl]-acetic acid tert-butyl ester (5b) was synthesized from 4 and allyl bromide by the method and chromatography used to prepare 5a to afford 388 mg (91% yield) of the title compound. <sup>1</sup>H-NMR (500MHz, CDCl<sub>3</sub>) δ 1.40 (s, 9H), 2.35-2.45 (m, 1H), 2.48-2.52 (m, 1H), 3.42-3.50 (m, 1H), 3.63-3.70 (m, 1H), 3.82-3.90 (m, 2H), 4.65-4.67 (d, 1H), 4.70-4.77 (q, 1H), 5.35-5.42 (m, 2H), 6.00-6.10 (m, 1H), 7.71-7.74 (d, 2H), 7.82-7.85 (d, 2H). Analytical HPLC: 13.28. LC-MS (ES<sup>+</sup>): m/e = 428 (M+H<sup>+</sup>).

Preparation of [6-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-3,7-dioxo-2-propyl-[1,2]diazepan-1-yl]-acetic acid tert-butyl ester (5c). A mixture of [2-allyl-6-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-3,7-dioxo-[1,2]diazepan-1-yl]-acetic acid tert-butyl ester (5b) (380 mg, 0.89 mmol) and 20% palladium (II) hydroxide on carbon (Pearlman's catalyst) (80 mg) in ethanol (10 mL) was stirred under hydrogen atmosphere for 3 hours. The reaction mixture

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was filtered through Celite and the filtrate was evaporated in vacuo to give 380 mg (99.5% yield) of the title compound.  $^1\text{H-NMR}$  (500MHz,  $\text{CDCl}_3$ )  $\delta$  1.05-1.09 (t, 3H), 1.47 (s, 9H), 1.71-1.82 (m, 2H), 2.33-2.46 (m, 1H), 2.46-2.53 (m, 1H), 3.00-3.09 (m, 1H), 3.43-3.60 (m, 2H), 3.95-4.00 (d, 1H), 4.10-4.18 (m, 1H), 4.54-4.58 (d, 1H), 5.40-5.45 (m, 1H), 7.70-7.76 (m, 2H), 7.80-7.85 (m, 2H). Analytical HPLC: 13.53 min. LC-MS (ES $^+$ ): m/e = 430 ( $\text{M}+\text{H}^+$ ).

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**Preparation of (6-Amino-2-benzyl-3,7-dioxo-[1,2]diazepan-1-yl)-acetic acid tert-butyl ester (6a).** A solution of [2-benzyl-6-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-3,7-dioxo-[1,2]diazepan-1-yl]-acetic acid tert-butyl ester (5a) (150 mg, 0.31 mmol) and hydrazine monohydrate (17.3 mg, 35 mmol) in ethanol (1.5 mL) was stirred at room temperature for 6 hours. Solvent was removed in vacuo. The residue was taken up into acetic acid (1.5 mL) and stirred at room temperature for 30 min. The mixture was evaporated in vacuo and the resulting residue was dissolved in ethyl acetate (20 mL), washed with 5%  $\text{Na}_2\text{CO}_3$  then water. The aqueous solution was extracted with ethyl acetate (20 mL x 2). The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$  and filtered. The filtrate was evaporated to dryness in vacuo to afford 107 mg (98% yield) of the title compound.  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.45 (s, 9H), 1.70-1.78 (m, 1H), 2.30-2.48 (m, 2H), 3.10-3.15 (m 1H), 3.30-3.38 (m, 1H), 3.95-4.00 (d, 1H), 4.36-4.40 (d, 1H), 4.45-4.49 (d, 1H), 5.07-5.12 (d, 1H), 7.28-7.38 (m, 5H). Analytical HPLC: 8.03 min. LC-MS (ES $^+$ ): m/e = 348 ( $\text{M}+\text{H}^+$ ).

(6-Amino-3,7-dioxo-2-propyl-[1,2]diazepan-1-yl)-acetic acid tert-butyl ester (6c) was prepared from 5c by the method used to prepare 6a to afford 182 mg (69% yield) of

the title compound.  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  0.94-1.01 (t, 3H), 1.50 (s, 9H), 1.55-1.67 (m, 2H), 1.70-1.80 (m, 1H), 2.30-2.37 (m, 1H), 2.50-2.60 (m, 1H), 3.10-3.18 (m, 1H), 3.21-3.28 (m, 1H), 3.81-3.87 (m, 1H), 3.91-3.98 (m, 1H), 4.10-4.15 (d, 1H), 4.39-4.43 (d, 1H). Analytical HPLC: 6.10 min. LC-MS ( $\text{ES}^+$ ): m/e = 300 ( $\text{M}+\text{H}^+$ ).

**Preparation of {2-Benzyl-6-[(isoquinoline-1-carbonyl)-amino]-3,7-dioxo-[1,2]diazepan-1-yl}-acetic acid tert-butyl ester (7a).** To a solution of isoquinoline-1-carbonic acid (173 mg, 1 mmol) in dichloromethane (5 mL) was added HOBT (135 mg, 1 mmol) followed by EDC (192 mg, 1 mmol) at 0°C. The mixture was stirred for 15 min and a solution of (6-amino-2-benzyl-3,7-dioxo-[1,2]diazepan-1-yl)-acetic acid tert-butyl ester (6a) (105 mg, 0.30 mmol) in dichloromethane (5 mL) was added. The reaction was stirred at 0°C for 30 min then at room temperature for 16 hours. The mixture was diluted with dichloromethane (50 mL) and washed with water (50 mL x 3). The organic layer was dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and evaporated in vacuo to give a pale yellow solid, that was purified by flash chromatography using dichloromethane/ethyl acetate (95/5 to 85/15) to afford 128 mg (84% yield) of the title compound.  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.49 (s, 9H), 2.02-2.10 (m, 1H), 2.50-2.57 (m, 1H), 2.88-2.97 (m, 1H), 3.60-3.70 (m, 1H), 3.84-3.89 (d, 1H), 4.52-4.57 (d, 1H), 4.84-4.98 (m, 3H), 7.26-7.42 (m, 5H), 7.64-7.84 (m, 4H), 8.45 (d, 1H), 8.76 (d, 1H), 9.44 (d, 1H). Analytical HPLC: 14.20 min. LC-MS ( $\text{ES}^+$ ): m/e = 503 ( $\text{M}+\text{H}^+$ ).

**[6-(Isoquinoline-1-carbonylamino)-3,7-dioxo-2-propyl-[1,2]diazepan-1-yl]-acetic acid tert-butyl ester (7b)** was prepared from (6-amino-3,7-dioxo-2-propyl-[1,2]diazepan-1-yl)-acetic acid tert-butyl ester (6c) and isoquinoline-1-carbonic acid by the method and chromatography used to

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- prepare 7a to afford 234 mg (86% yield) of the title compound.  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.01-1.07 (t, 3H), 1.49 (s, 9H), 1.73-1.82 (m, 1H), 2.03-2.12 (m, 1H), 2.42-2.50 (m, 1H), 2.84-2.93 (m, 1H), 3.15-3.22 (m, 1H), 3.50-3.58 (m, 1H), 4.03-4.15 (m, 2H), 4.60-4.63 (d, 1H), 5.23-5.30 (m, 1H), 7.64-7.83 (m, 2H), 7.80-7.88 (m, 2H), 8.50 (d, 1H), 8.87 (d, 1H), 9.55 (d, 1H). Analytical HPLC: 10.45 min. LC-MS ( $\text{ES}^+$ ): m/e = 455 ( $\text{M}+\text{H}^+$ ).
- 10 [6-(4-Allyloxy-3,5-dichloro-benzoylamino)-3,7-dioxo-2-propyl-[1,2]diazepan-1-yl]-acetic acid tert-butyl ester (7c) was prepared from (6-amino-3,7-dioxo-2-propyl-[1,2]diazepan-1-yl)-acetic acid tert-butyl ester (6c) and 3,5-dichloro-4-allyloxy-benzoyl acid by the method and chromatography used to prepare 7a to afford 200 mg (72% yield) of the title compound.  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  0.96-1.00 (t, 3H), 1.50 (s, 9H), 1.64-1.73 (m, 2H), 1.90-1.97 (m, 1H), 2.40-2.45 (m, 1H), 2.83-2.92 (m, 1H), 3.10-3.17 (m, 1H), 3.40-3.49 (m, 1H), 4.02-4.10 (m, 2H), 4.48-4.51 (d, 1H), 4.60-4.63 (m, 2H), 5.11-5.18 (m, 1H), 5.30-5.34 (d, 1H), 5.40-5.44 (d, 1H), 6.10-6.18 (m, 1H), 7.86-7.89 (d, 1H), 7.73 (s, 2H). Analytical HPLC: 10.47 min. LC-MS ( $\text{ES}^+$ ): m/e = 528, 530 ( $\text{M}+\text{H}^+$ ).
- 15 25 Preparation of Isoquinoline-1-carboxylic acid {1-benzyl-2-[(2-benzyloxy-5-oxo-tetrahydro-furan-3-ylcarbamoyl)-methyl]-3,7-dioxo-[1,2]diazepan-4-yl}-amide (10a). {2-Benzyl-6-[(isoquinoline-1-carbonyl)-amino]-3,7-dioxo-[1,2]diazepan-1-yl}-acetic acid tert-butyl ester (7a) (115 mg, 0.23 mmol) was stirred in 20% of trifluoroacetic acid (TFA) in dichloromethane (2 mL) overnight. The solution was evaporated to afford {2-benzyl-6-[(isoquinoline-1-carbonyl)-amino]-3,7-dioxo-[1,2]diazepan-1-yl}-acetic acid (8a).  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  2.05-2.11 (m, 1H), 2.45-2.50 (m, 1H), 2.72-2.83
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(m, 1H), 3.45-3.54 (m, 1H), 4.01-4.06 (d, 1H), 4.59-4.63 (d, 1H), 4.70-4.82 (m, 2H), 4.93-4.98 (d, 1H), 7.28-7.42 (m, 5H), 7.80-8.10 (m, 4H), 8.40-8.52 (m, 2H), 8.85 (d, 1H). The acid (**8a**) was dissolved in dichloromethane (2 mL) followed by addition of HOBT (77 mg, 0.57 mmol) and EDC (110 mg, 0.57 mmol) and stirred for 30 min. A solution of (2-benzyloxy-5-oxo-tetrahydro-furan-3-yl)-carbamic acid allyl ester (**9**, anti diastereomer) (166 mg, 0.57 mmol) in dichloromethane/DMF (3/1 mL), charged with 1,3-dimethylbarbituric acid (DMBA) (90 mg, 0.57 mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (66 mg, 0.057 mmol) for 30 min, was added and the resulting mixture was stirred at room temperature for 16 hours. The reaction mixture was diluted with ethyl acetate (100 mL) and washed with water (50 mL x 3), dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to give a pale yellow solid, that was purified by flash chromatography using dichloromethane/methanol (99.5/0.5 to 98.5/1.5) to afford 97.5 mg (67% yield) of the title compound. <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ 2.03-2.13 (m, 1H), 2.40-2.43 (d, 1H), 2.55-2.60 (m, 1H), 2.83-2.92 (m, 1H), 3.04-3.10 (q, 1H), 3.28-3.38 (m, 1H), 4.08-4.11 (d, 1H), 4.20-4.24 (d, 1H), 4.38-4.41 (m, 1H), 4.67-4.70 (d, 1H), 4.78-4.87 (m, 2H), 4.91-5.02 (m, 2H), 5.36 (s, 1H), 6.05 (d, 1H), 7.20-7.38 (m, 10H), 7.68-7.78 (m, 2H), 7.80-7.88 (m, 2H), 8.48 (d, 1H), 8.70 (d, 1H), 9.49 (d, 1H). Analytical HPLC: 12.53 min. LC-MS (ES<sup>+</sup>): m/e = 636 (M+H<sup>+</sup>).

Isoquinoline-1-carboxylic acid {2-[(2-benzyloxy-5-oxo-tetrahydro-furan-3-ylcarbamoyl)-methyl]-3,7-dioxo-1-propyl-[1,2]diazepan-4-yl}-amide (**10b**) was synthesized from **7b** and the diastereomers of **9** by the method and chromatography used to prepare **10a** to afford both *syn* diastereomer (203 mg, 67% yield, higher R<sub>f</sub>) and *anti* diastereomer (93 mg, 31% yield, lower R<sub>f</sub>) of the title compound. <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) for the *anti*

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diastereomer:  $\delta$  0.96-1.05 (t, 3H), 1.72-1.82 (m, 2H),  
2.10-2.20 (m, 1H), 2.48-2.56 (m, 2H), 2.78-2.86 (m, 1H),  
2.92-3.18 (m, 3H), 3.25-3.39 (m, 1H), 3.95-4.02 (m, 1H),  
4.06-4.17 (m, 1H), 4.41-4.50 (m, 1H), 4.62-4.66 (d, 1H),  
5 4.82-4.89 (d, 1H), 5.10-5.20 (m, 1H), 5.5 (s, 1H), 6.68  
(d, 1H) 7.28-7.40 (m, 5H), 7.70-7.77 (m, 2H), 7.82-7.89  
(m, 2H), 8.51 (d, 1H), 8.77 (d, 1H), 9.52 (d, 1H); for  
the *syn* diastereomer:  $\delta$  0.90-0.98 (t, 3H), 1.60-1.80 (m,  
2H), 2.00-2.10 (m, 1H), 2.43-2.50 (m, 2H), 2.80-2.98 (m,  
10 2H), 3.10-3.20 (m, 2H), 4.03-4.17 (m, 2H), 4.29-4.33 (d,  
1H), 4.60-4.63 (d, 1H), 4.70-4.79 (m, 1H), 4.85-4.89 (d,  
1H), 5.21-5.30 (m, 1H), 5.52 (d, 1H), 6.70 (d, 1H), 7.28-  
7.33 (m, 5H), 7.64-7.78 (m, 2H), 7.83-7.90 (m, 2H), 8.50  
(d, 1H), 8.85 (d, 1H), 9.50 (d, 1H). Analytical HPLC:  
15 10.60 min for the anti diastereomer and 10.30 min for the  
*syn* diastereomer. LC-MS (ES<sup>+</sup>) for the mixture of the  
product: m/e = 588 (M+H<sup>+</sup>).

20 **4-Allyloxy-N-{2-[{(2-benzyloxy-5-oxo-tetrahydro-furan-3-yl)carbamoyl}-methyl]-3,7-dioxo-1-propyl-[1,2]diazepan-4-yl}-3,5-dichloro-benzamide (10c)** was synthesized from 7c  
and the diastereomers of 9 by the method and  
chromatography used to prepare 10a to afford both anti  
diastereomer (78 mg, 31% yield, lower Rf) and *syn*  
25 diastereomer (129 mg, 52% yield, higher Rf) of the title  
compound. <sup>1</sup>H-NMR (500Hz, CDCl<sub>3</sub>) for the anti diastereomer:  
 $\delta$  1.00-1.05 (t, 3H), 1.60-1.80 (m, 2H), 2.03-2.18 (m,  
1H), 2.23-2.30 (d, 1H), 2.40-2.48 (m, 1H), 2.62-2.78 (m,  
1H), 2.90-3.12 (m, 2H), 3.50-3.60 (m, 1H), 4.05-4.25 (m,  
30 3H), 4.48-4.52 (m, 1H), 4.60-4.68 (m, 3H), 4.80-44.85 (d,  
1H), 5.08-5.20 (m, 1H), 5.30-5.39 (m, 2H), 5.40-5.45 (d,  
1H), 6.08-6.20 (m, 1H), 6.82-6.85 (d, 1H), 7.30-7.45 (m,  
6H), 7.85 (s, 2H); for the *syn* diastereomer:  $\delta$  0.94-1.04  
(t, 3H), 1.60-1.72 (m, 2H), 1.85-1.93 (m, 1H), 2.31-2.40  
35 (m, 1H), 2.41-2.51 (m, 1H), 2.72-2.82 (m, 1H), 2.83-2.95

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(m, 1H), 3.00-3.09 (m, 1H), 3.17-3.30 (m, 1H), 3.99-4.10  
(m, 1H), 4.10-4.18 (d, 1H), 4.21-4.30 (d, 1H), 4.58-4.65  
(m, 3H), 4.70-4.78 (m, 1H), 4.85-4.90 (d, 1H), 5.05-5.15  
(m, 1H), 5.28-5.35 (d, 1H), 5.40-5.45 (d, 1H), 5.53 (d,  
5 1H), 6.08-6.17 (m, 1H), 6.55-6.60 (d, 1H), 6.75-6.80 (d,  
1H), 7.27-7.40 (m, 3H), 7.40-7.55 (m, 1H), 7.60-7.70 (m,  
1H), 7.73 (s, 2H). Analytical HPLC for diastereomers of  
the title compound: 10.26 min. LC-MS (ES<sup>+</sup>) for the  
mixture of the product: m/e = 661, 663 (M+H<sup>+</sup>).

10

Preparation of *N*-{2-[(2-Benzyl-oxo-tetrahydro-furan-3-ylcarbamoyl)-methyl]-3,7-dioxo-1-propyl-[1,2]diazepan-4-yl}-3,5-dichloro-4-hydroxy-benzamide (10d). To a solution of 4-allyloxy-*N*-{2-[(2-benzyloxy-5-oxo-tetrahydro-furan-3-ylcarbamoyl)-methyl]-3,7-dioxo-1-propyl-[1,2]diazepan-4-yl}-3,5-dichloro-benzamide (10c, diastereomers) (103 mg, 0.16 mmol) in dichloromethane (15 mL) was added DMBA followed by Pd(PPh<sub>3</sub>)<sub>4</sub> (30 mg, 0.026 mmol), stirred at room temperature for 7 hours. The reaction mixture was washed with water, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and purified by flash chromatography using dichloromethane/methanol (99.5/0.5 to 97/3) to afford both *anti* diastereomer (18 mg, 18% yield, lower R<sub>f</sub>) and *syn* diastereomer (48 mg, 50% yield, higher R<sub>f</sub>) of the title compound. <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) for the *anti* diastereomer: δ 0.9-1.02 (m, 3H), 1.65-1.85 (m, 2H), 2.01-2.18 (m, 0.5H), 2.20-2.30 (d, 0.5H), 2.37-2.47 (m, 1H), 2.58-2.70 (m, 1H), 2.90-3.00 (m, 1H), 3.00-3.10 (m, 1H), 3.25-3.50 (m, 1H), 4.0-4.15 (m, 2H), 4.15-4.25 (d, 1H), 4.40-4.55 (m, 1H), 4.55-4.67 (m, 1H), 4.72-4.82 (d, 1H), 5.05-5.17 (m, 1H), 5.27-5.38 (m, 2H), 6.90-7.00 (d, 1H), 7.25-7.40 (m, 6H), 7.60-7.70 (m, 1H), 7.80 (s, 2H; for the *syn* diastereomer: δ 0.9-1.00 (m, 3H), 1.50-1.70 (m, 2H), 1.8-1.92 (m, 1H), 2.38-2.42 (m, 1H), 2.48-2.58 (m, 1H), 2.74-2.87 (m, 1H), 2.88-2.98 (m, 1H),

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3.00-3.13 (m, 1H), 3.17-3.30 (m, 1H), 4.00-4.12 (m, 1H),  
4.14-4.30 (d, 1H), 4.22-4.32 (m, 1H), 4.62-4.46 (d, 1H),  
4.75-4.80 (m, 1H), 4.90-4.95 (d, 1H), 5.10-5.20 (m, 1H),  
5.53-5.57 (d, 1H), 6.24 (s, 1H), 6.49 (d, 1H), 6.70 (d,  
5 1H), 7.25-7.40 (m, 5H), 7.71 (s, 2H). Analytical HPLC:  
8.55 min for *syn* diastereomer and 8.57 min for the *anti*  
diastereomer. LC-MS (ES<sup>+</sup>) for the mixture of the  
product: m/e = 621, 623 (M+H<sup>+</sup>).

10 **Preparation of 3-(2-{2-Benzyl-6-[(isoquinoline-1-carbonyl)-amino]-3,7-dioxo-[1,2]diazepan-1-yl}-acetylamino)-4-oxo-butyric acid (11a).** Isoquinoline-1-carboxylic acid {1-benzyl-2-[(2-benzyloxy-5-oxo-tetrahydro-furan-3-ylcarbamoyl)-methyl]-3,7-dioxo-[1,2]diazepan-4-yl}-amide (10a, diastereomers) (14 mg, 0.022 mmol) was stirred in the solution of 10% HCl (1.5 mL) and acetonitrile (1 mL) for 4 hours. The reaction mixture was diluted with water (30 mL), washed with ether (30 mL) twice. The aqueous solution was purged with nitrogen for 30 min then cooled in dry ice and lyophilized overnight to afford 10 mg (83% yield) of the title compound. <sup>1</sup>H-NMR (500 MHz, CD<sub>3</sub>OD) δ 2.00-2.10 (m, 1H), 2.32-2.50 (m, 2H), 3.62-3.72 (m, 1H), 4.15-4.35 (m, 2H), 4.45-4.80 (m, 4H), 5.25-5.32 (m, 1H), 7.30-7.68 (m, 5H), 7.95-8.05 (m, 1H), 8.12-8.17 (m, 1H), 8.22-8.27 (m, 1H), 8.35-8.41 (d, 1H), 8.56 (s, 1H), 8.65-8.74 (d, 1H). Analytical HPLC: 9.40 min. LC-MS (ES<sup>+</sup>): m/e = 546 (M+H<sup>+</sup>).

30 **3-(2-{6-[(Isoquinoline-1-carbonyl)-amino]-3,7-dioxo-2-propyl-[1,2]diazepan-1-yl}-acetylamino)-4-oxo-butyric acid (11b)** was prepared from isoquinoline-1-carboxylic acid {2-[(2-benzyloxy-5-oxo-tetrahydro-furan-3-ylcarbamoyl)-methyl]-3,7-dioxo-1-propyl-[1,2]diazepan-4-yl}-amide (10b, diastereomers) (95 mg, 0.16 mmol) by the method used to prepare 11a to afford 28 mg (35% yield) of

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the title compound.  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3/\text{CD}_3\text{OD} = 0.5$  mL/3 drops)  $\delta$  0.90-1.00 (t, 3H), 1.65-1.80 (m, 2H), 2.10-2.28 (m, 1H), 2.32-2.40 (m, 1H), 2.47-2.80 (m, 3H), 3.05-3.18 (m, 1H), 3.30-3.51 (m, 2H), 4.00-4.55 (m, 3H), 5.10-5.20 (m, 1H), 7.75-8.05 (m, 4H), 8.49 (s, 1H), 8.90-9.00 (m, 1H). Analytical HPLC: 6.26 min. LC-MS (ES $^+$ ): m/e = 498 ( $\text{M}+\text{H}^+$ ).

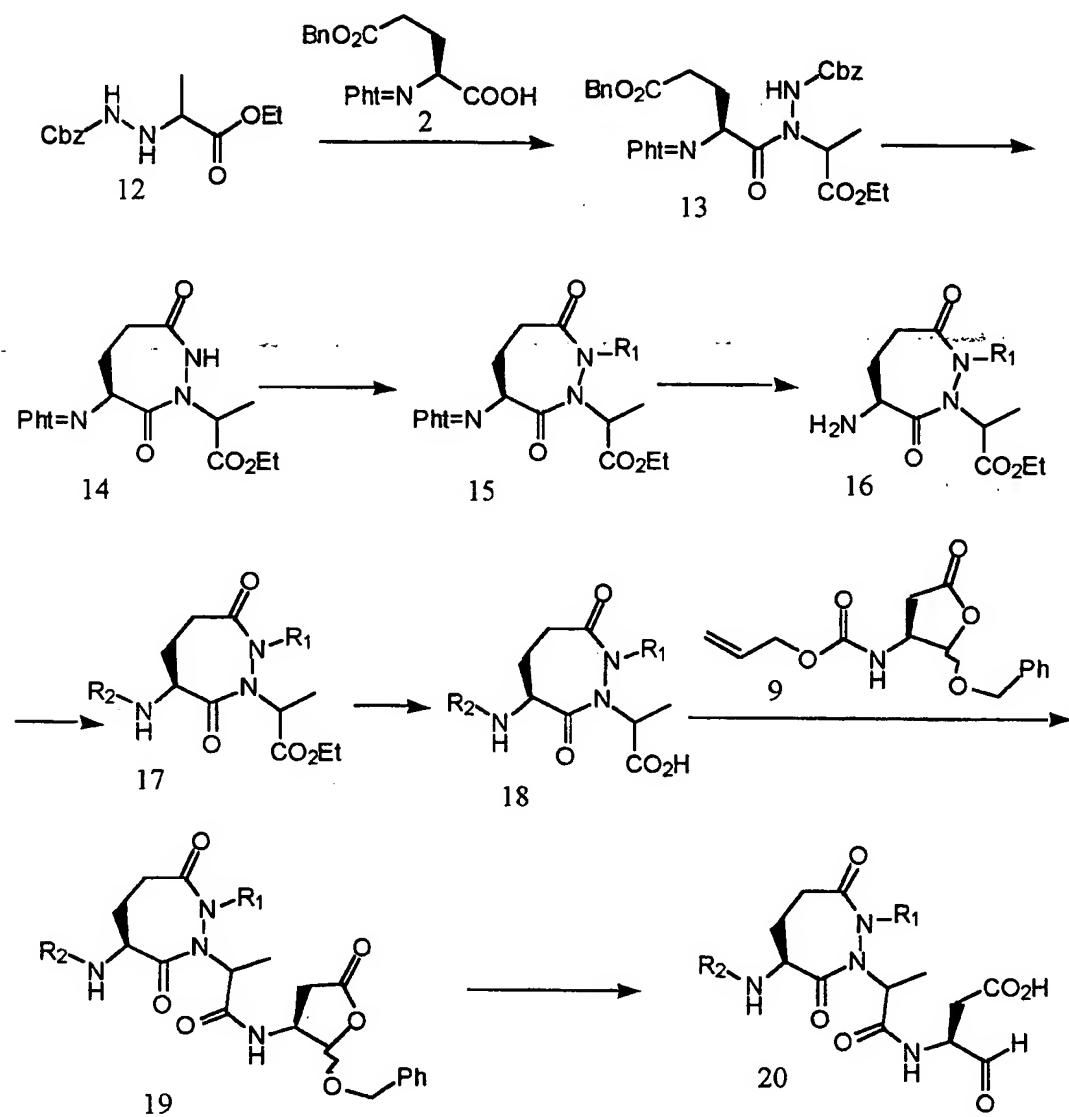
3-{2-[6-(3,5-Dichloro-4-hydroxy-benzoylamino)-3,7-dioxo-2-propyl-[1,2]diazepan-1-yl]-acetylaminio}-4-oxo-butyric acid (11c) was prepared from N-{2-[2-benzyloxy-5-oxo-tetrahydro-furan-3-ylcarbamoyl]-methyl}-3,7-dioxo-1-propyl-[1,2]diazepan-4-yl}-3,5-dichloro-4-hydroxy-benzamide (10d, diastereomers) (30 mg, 0.05 mmol) by the method used to prepare 11a to afford 19 mg (74% yield) of the title compound.  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3/\text{CD}_3\text{OD} = 0.5$  mL/3 drops)  $\delta$  0.90-0.95 (t, 3H), 1.60-1.70 (m, 2H), 2.00-2.10 (m, 1H), 2.25-2.36 (m, 1H), 2.48-2.82 (m, 3H), 2.98-3.10 (m, 1H), 3.20-3.35 (m, 1H), 3.90-4.50 (m, 4H), 4.95-5.08 (m, 1H), 7.62-7.72 (m, 2H). Analytical HPLC: 5.40 min. LC-MS (ES $^+$ ): m/e = 531, 533 ( $\text{M}+\text{H}^+$ ).

3-{2-[6-(3,5-Dichloro-4-hydroxy-benzoylamino)-3,7-dioxo-2-methyl-[1,2]diazepan-1-yl]-acetylaminio}-4-oxo-butyric acid (11d) was prepared according to the method used to prepare (11c) only substituting iodomethane for allyl bromide.

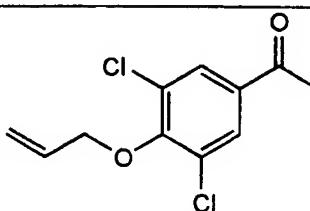
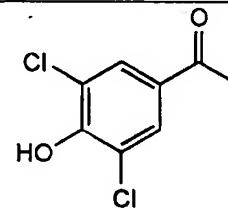
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Example 6

Compounds 19 and 20 were prepared as described below:



Compounds	R <sub>1</sub>
15	Me
16	Me

Compounds	R <sub>1</sub>	R <sub>2</sub>
17		
18	Me	
19		
20	Me	

- 5     **Preparation of 2-(N'-Benzylloxycarbonyl-hydrazino)-**  
**propionic acid ethyl ester (12).** To a solution of benzyl  
 carbamate (665 mg, 4 mmol), triethylamine (1.11 mL) in  
 dichloromethane (4 mL) was added dropwise ethyl O-  
 trifluoromethanesulfonyl-D-lactate at 0°C. The solution  
 10    was stirred at 0°C for 15 min then at room temperature  
 for 16 hours. The mixture was diluted with  
 dichloromethane (100 mL), washed with water (50 mL x 2),  
 1% HCl (50 mL x 2). The organic layer was dried over  
 anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated to dryness in  
 15    vacuo to give 570 mg (54% yield) of the title compound.  
<sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ 1.25-1.40 (m, 6H), 3.68-3.78 (m,  
 1H), 4.12-4.20 (m, 3H), 5.07-5.15 (m, 1H), 6.45-6.57 (m,  
 1H), 7.30-7.45 (m, 5H). Analytical HPLC: 5.56 min. LC-MS  
 (ES<sup>+</sup>): m/e = 267 (M+H<sup>+</sup>).  
 20    **5-[N'-Benzylloxycarbonyl-N-(1-ethoxycarbonyl-ethyl)-**  
**hydrazino]-4-(1,3-dioxo-1,3-dihydro-isooindol-2-yl)-5-oxo-**

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pentanoic acid benzyl ester (13) was prepared from 2-(N'-benzyloxycarbonyl-hydrazino)-propionic acid ethyl ester (12) and 2 by the method and chromatography used to prepare 3 to afford 850 mg (64% yield) of the title compound.  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.10-1.50 (m, 6H), 2.40-2.70 (m, 5H), 4.05-4.30 (m, 2H), 4.65-4.70 (d, 0.5H), 4.80-4.86 (d, 0.5H), 5.00-5.40 (m, 5H), 7.15-7.50 (m, 10H), 7.65-7.90 (m, 4H). Analytical HPLC: 9.00 min. LC-MS (ES $^+$ ): m/e = 616 ( $\text{M}+\text{H}^+$ ).

10

2-[6-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-3,7-dioxo-[1,2]diazepan-1-yl]-propionic acid tert-butyl ester (14) was prepared from 5-[N'-benzyloxycarbonyl-N-(1-ethoxycarbonyl-ethyl)-hydrazino]-4-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-5-oxo-pentanoic acid benzyl ester (13) by the method and chromatography used to prepare 4 to afford 318 mg (64% yield) of the title compound.  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.25-1.35 (m, 3H), 1.50-1.60 (m, 3H), 2.37-2.55 (m, 2H), 2.75-2.95 (m, 1H), 3.35-3.65 (m, 2H), 4.15-4.30 (m, 2H), 5.15-5.40 (m, 1H), 5.47-5.60 (m, 1H), 7.65-7.90 (m, 4H). Analytical HPLC: 5.60 min. LC-MS (ES $^+$ ): m/e = ( $\text{M}+\text{H}^+$ ).

Preparation of 2-[6-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-2-methyl-3,7-dioxo-[1,2]diazepan-1-yl]-propionic acid ethyl ester (15). A mixture of 2-[6-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-3,7-dioxo-[1,2]diazepan-1-yl]-propionic acid tert-butyl ester (14) (314 mg, 0.84 mmol), benzyltriethylammonium chloride (30 mg, 0.13 mmol),  $\text{K}_2\text{CO}_3$  (406 mg, 2.94 mmol) and iodomethane (360 mg, 2.53 mmol) in THF (8 mL) was stirred at room temperature for five days. The mixture was diluted with dichloromethane (70 mL), washed with water three times, dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and evaporated *in vacuo* to dryness to afford 296 mg (91% yield) of the title compound as a

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mixture of diastereomers.  $^1\text{H-NMR}$  (500MHz,  $\text{CDCl}_3$ )  $\delta$  1.25-1.35 (m, 2.5H), 1.47-1.52 (m, 0.5H), 1.60-1.75 (m, 3H), 2.37-2.52 (m, 2H), 3.05-3.14 (m, 0.5H), 3.30-3.45 (m, 3.5H), 3.45-3.58 (m, 1H), 4.14-4.28 (m, 2H), 4.52-4.58 (m, 0.5H), 4.80-4.87 (m, 0.5H), 5.13-5.28 (m, 1H), 7.70-7.90 (m, 4H). Analytical HPLC: 6.00 and 6.11 min. LC-MS ( $\text{ES}^+$ ): m/e = 388 ( $\text{M}+\text{H}^+$ ).

2-(6-Amino-2-methyl-3,7-dioxo-[1,2]diazepan-1-yl)-propionic acid ethyl ester (16) was prepared from 2-[6-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-2-methyl-3,7-dioxo-[1,2]diazepan-1-yl]-propionic acid ethyl ester (15) by the method used to prepare 6a to afford 143 mg (73% yield) of the title compound as a mixture of diastereomers.  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.22-1.30 (m, 2.5H), 1.47-1.50 (d, 0.5H), 1.52-1.70 (m, 3H), 1.70-1.82 (m, 1H), 2.30-2.40 (m, 1H), 2.48-2.69 (m, 1H), 2.75-2.82 (m, 0.5H), 3.03-3.11 (m, 0.5H), 3.22 (d, 3H), 3.61-3.75 (m, 1H), 4.18-4.30 (m, 2H), 4.49-4.54 (m, 0.5H), 4.85-4.90 (m, 0.5H). Analytical HPLC: 3.90 and 4.06 min. LC-MS ( $\text{ES}^+$ ): m/e = 258 ( $\text{M}+\text{H}^+$ ).

2-[6-(4-Allyloxy-3,5-dichloro-benzoylamino)-2-methyl-3,7-dioxo-[1,2]diazepan-1-yl]-propionic acid ethyl ester (17) was prepared from 2-(6-amino-2-methyl-3,7-dioxo-[1,2]diazepan-1-yl)-propionic acid ethyl ester (16) and 3,5-dichloro-4-allyloxy-benzoyl acid by the method and chromatography used to prepare 7a to afford 216 mg (80% yield) of the title compound as a mixture of diastereomers.  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.22-1.40 (m, 3H), 1.50-1.80 (m, 3H), 1.80-1.95 (m, 1H), 2.40-2.50 (m, 1H), 2.82-3.02 (m, 2H), 3.10-3.40 (m, 4H), 4.20-4.35 (m, 2H), 4.50-5.01 (m, 3H), 5.25-5.45 (m, 2H), 6.05-6.20 (m, 1H), 6.90-7.00 (m, 2H), 7.70-7.80 (d, 2H). Analytical

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HPLC: 6.97 and 7.06 min. LC-MS (ES<sup>+</sup>): m/e = 486, 488 (M+H<sup>+</sup>).

**Preparation of 2-[6-(4-Allyloxy-3,5-dichloro-**

5 **benzoylamino)-2-methyl-3,7-dioxo-[1,2]diazepan-1-yl]-**  
**propionic acid (18). 2-[6-(4-Allyloxy-3,5-dichloro-**  
**benzoylamino)-2-methyl-3,7-dioxo-[1,2]diazepan-1-yl]-**  
10 **propionic acid ethyl ester (17) (216 mg, 0.44 mmol) was**  
**stirred in 1N NaOH (2 mL) and MeOH (2 mL) at room**  
**temperature for 45 min. The mixture was diluted with**  
**water (30 mL), extracted with dichloromethane three**  
**times.... The combined organic layers were dried over**  
**anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated in vacuo to**  
**dryness to afford 201 mg (99% yield) of the title**  
15 **compound.** <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ 1.58-1.68 (m, 3H),  
1.88-2.00 (m, 1H), 2.40-2.48 (m, 1H), 2.80-3.18 (m, 2H),  
3.25-3.48 (d, 3H), 4.47-4.65 (m, 2.5H), 4.74-4.81 (m,  
0.5H), 4.90-5.05 (m, 1H), 5.27-5.31 (d, 1H), 5.38-5.43  
(d, 1H), 6.08-61.8 (m, 1H), 7.07-7.22 (m, 2H), 7.71 (d,  
2H). Analytical HPLC: 5.85 min. LC-MS (ES<sup>+</sup>): m/e =  
20 458, 460 (M+H<sup>+</sup>).

**Preparation of N-{2-[1-(2-Benzyl-5-oxo-tetrahydro-**

25 **furan-3-ylcarbamoyl)-ethyl}-1-methyl-3,7-dioxo-**  
**[1,2]diazepan-4-yl}-3,5-dichloro-4-hydroxy-benzamide**  
**(19). To a solution of 2-[6-(4-allyloxy-3,5-dichloro-**  
**benzoylamino)-2-methyl-3,7-dioxo-[1,2]diazepan-1-yl]-**  
**propionic acid (18) (183 mg, 0.40 mmol) in**  
**dichloromethane was added HOBT (65 mg, 0.48 mmol)**  
30 **followed by EDC (123 mg, 0.64 mmol). The mixture was**  
**stirred at 0°C for 30 min, then a solution of (2-**  
**benzyloxy-5-oxo-tetrahydro-furan-3-yl)-carbamic acid**  
**allyl ester (9, anti diastereomer) (140 mg, 0.48 mmol) in**  
**dichloromethane, charged with 1,3-dimethylbarbituric acid**  
35 **(DMBA) (75 mg, 0.48 mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (60 mg, 0.05 mmol)**

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for 30 min, was added and the resulting mixture was stirred at room temperature for 5 hours. The second portion of DMBA (63 mg, 0.40 mmol) was added and the reaction mixture was continuously stirred at room 5 temperature for 16 hours. The reaction was quenched with water and extracted with dichloromethane. The organic layer was dried over anhydrous  $\text{Na}_2\text{SO}_4$ , filtered and evaporated to give a pale yellow solid, that was purified by flash chromatography using dichloromethane/methanol 10 (99/1 to 95/5) to afford 70 mg (29% yield) of the title compound as a mixture of diastereomers.  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.39-1.45 (m, 3H), 2.60-2.80 (m, 2H), 2.80-3.10 (m, 1H), 3.12-3.32 (m, 4H), 4.20-4.62 (m, 2H), 4.70-4.88 (m, 2H), 5.25-5.45 (m, 1H), 6.65-6.95 (m, 3H), 7.20-7.50 (m, 5H), 7.61 (s, 1H), 7.72 (d, 1H). Analytical HPLC: 15 10.86 and 10.98 min. LC-MS ( $\text{ES}^+$ ): m/e = 607, 609 ( $\text{M}+\text{H}^+$ ).

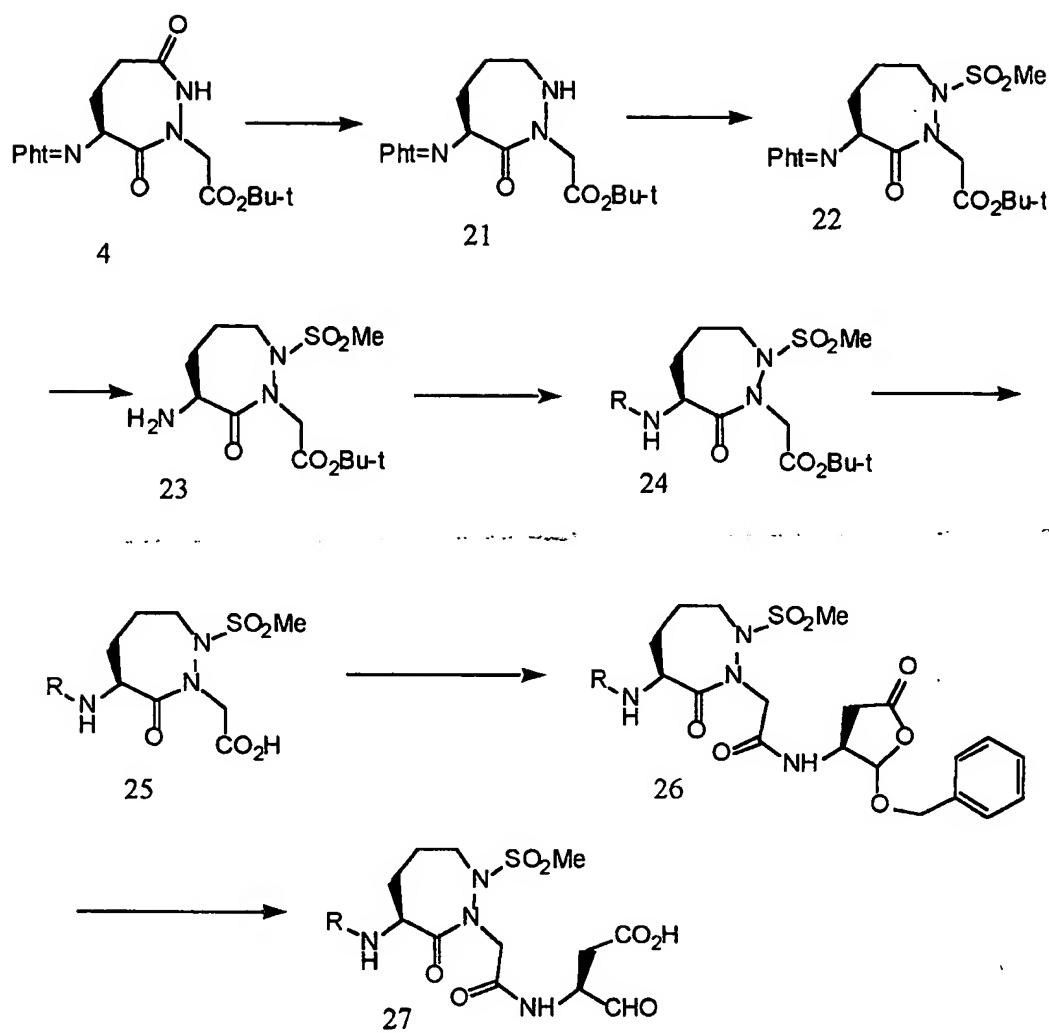
3-{2-[6-(3,5-Dichloro-4-hydroxy-benzoylamino)-2-methyl-  
3,7-dioxo-[1,2]diazepan-1-yl]-propionylamino}-4-oxo-  
butyric acid (20) was prepared from N-{2-[1-(2-benzyloxy-  
20 5-oxo-tetrahydro-furan-3-ylcarbamoyl)-ethyl]-1-methyl-  
3,7-dioxo-[1,2]diazepan-4-yl}-3,5-dichloro-4-hydroxy-  
benzamide (19) (28 mg, 0.046 mmol) by the method used to  
prepare 11a, affording 17 mg (71% yield) of the title  
25 compound.  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3/\text{CD}_3\text{OD} = 0.5 \text{ mL}/3 \text{ drops}$ )  
 $\delta$  1.20-1.50 (m, 3H), 1.90-2.10 (m, 1H), 2.25-2.85 (m,  
4H), 3.10-3.40 (m, 3H), 4.05-4.50 (m, 1H), 4.55-4.65 (m,  
1H), 4.75-5.05 (m, 2H), 7.72-7.76 (m, 2H). Analytical  
HPLC: 7.51 min. LC-MS ( $\text{ES}^+$ ): m/e = 517, 519 ( $\text{M}+\text{H}^+$ ).

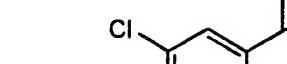
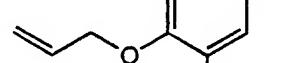
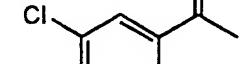
30

Example 7

Compound 27 was prepared as described below:

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Compounds	R
24	
25	
26a	
26b	
27	

**Preparation of [6-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-7-oxo-[1,2]diazepan-1-yl]-acetic acid tert-butyl ester (21).** To a solution of [6-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-3,7-dioxo-[1,2]diazepan-1-yl]-acetic acid 5 tert-butyl ester (4) (775 mg, 2.0 mmol) in THF (4 mL) was added borane-THF complex in THF (1M, 4 mL). The reaction was stirred at 0°C for 30 min then at room temperature for 3 hours. The mixture was diluted with ice-water (60 mL), extracted with ethyl acetate (60 mL x 3). The 10 combined organic layers were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated *in vacuo* to give a solid, that was purified by flash chromatography using hexane/ethyl acetate (95/5 to 70/30) to afford 585 mg (78% yield) of the title compound. <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) δ 1.43 (s, 9H), 1.78-1.90 (m, 1H), 2.00-2.15 (m, 2H), 2.65-2.78 (m, 1H), 2.95-3.07 (m, 1H), 3.22-3.30 (m, 1H), 3.85-3.92 (d, 1H), 4.30-4.42 (m, 2H), 5.39-5.42 (m, 1H), 7.62-7.71 (m, 2H), 7.79-7.86 (m, 2H). Analytical HPLC: 7.86 min. LC-MS (ES<sup>+</sup>): m/e = 374 (M+H<sup>+</sup>).

20 **Preparation of [6-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-2-methanesulfonyl-7-oxo-[1,2]diazepan-1-yl]-acetic acid tert-butyl ester (22).** To a solution of [6-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-7-oxo-[1,2]diazepan-1-yl]-acetic acid 25 tert-butyl ester (21) (155 mg, 0.42 mmol), triethylamine (0.5 mL) and 4-N,N-dimethylaminopyridine (DMAP) (101 mg, 0.50 mmol) in dichloromethane was added dropwise methanesulfonyl chloride (95 mg, 0.83 mmol). The mixture was stirred at 0°C for 5 min then at room 30 temperature for 16 hours. The mixture was quenched with water, extracted with dichloromethane. The organic solution was washed with water then brine, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and purified by flash chromatography using dichloromethane/ethyl acetate (99/1 to 95/5) to afford 154 mg (82% yield) of the title

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compound.  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.47 (s, 9H), 2.05-2.21 (m, 2H), 2.83-2.87 (m, 1H), 3.27 (s, 3H), 3.53-3.58 (m, 1H), 4.07-4.11 (d, 1H), 4.29-4.33 (m, 1H), 4.50-4.53 (d, 1H), 5.42-5.44 (m, 1H), 7.70-7.85 (m, 4H).

5 Analytical HPLC: 12.27 min. LC-MS ( $\text{ES}^+$ ): m/e = 452 ( $\text{M}+\text{H}^+$ ).

(6-Amino-2-methanesulfonyl-7-oxo-[1,2]diazepan-1-yl)-acetic acid tert-butyl ester (23) was prepared from [6-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-2-methanesulfonyl-7-oxo-[1,2]diazepan-1-yl]-acetic acid tert-butyl ester (22) by the method used to prepare 6a to afford 95 mg (89% yield) of the title compound.  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.48 (s, 9H), 1.66-1.71 (m, 1H), 1.83-1.87 (m, 1H), 1.94-1.98 (m, 1H), 2.09-2.13 (m, 1H), 3.07 (s, 3H), 3.45-3.51 (m, 1H), 3.87-3.91 (d, 1H), 4.00-4.11 (m, 2H), 4.59-4.63 (d, 1H). Analytical HPLC: 5.87 min. LC-MS ( $\text{ES}^+$ ): m/e = 322 ( $\text{M}+\text{H}^+$ ).

20 [6-(4-Allyloxy-3,5-dichloro-benzoylamino)-2-methanesulfonyl-7-oxo-[1,2]diazepan-1-yl]-acetic acid tert-butyl ester (24) was prepared from (6-amino-2-methanesulfonyl-7-oxo-[1,2]diazepan-1-yl)-acetic acid tert-butyl ester (23) and 3,5-dichloro-4-allyloxybenzoic acid by the method and chromatography used to prepare 7c to afford 193 mg (87% yield) of the title compound.  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.50 (s, 9H), 1.78-1.93 (m, 2H), 2.22-2.25 (m, 2H), 3.16 (s, 3H), 3.44-3.52 (m, 1H), 4.03-4.06 (d, 1H), 4.22-4.25 (d, 1H), 4.60-4.64 (m, 3H), 5.11-5.13 (m, 1H), 5.28-5.29 (d, 1H), 5.40-5.44 (m, 1H), 6.10-6.16 (m, 1H), 7.21-7.30 (m, 1H), 7.75 (s, 2H). Analytical HPLC: 7.39 min. LC-MS ( $\text{ES}^+$ ): m/e = 550, 552 ( $\text{M}+\text{H}^+$ ).

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[6-(4-Allyloxy-3,5-dichloro-benzoylamino)-2-methanesulfonyl-7-oxo-[1,2]diazepan-1-yl]-acetic acid

(25) was prepared from [6-(4-allyloxy-3,5-dichloro-benzoylamino)-2-methanesulfonyl-7-oxo-[1,2]diazepan-1-

5 yl]-acetic acid tert-butyl ester (24) by the method used to prepare 8a to afford 173 mg (100% yield) of the title compound.  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.74-1.77 (m, 1H), 1.91-1.93 (m, 1H), 2.22-2.25 (m, 2H), 3.19 (s, 3H), 3.39-3.44 (m, 1H), 4.24-4.28 (m, 2H), 4.61-4.63 (m, 2H), 4.71-4.75 (d, 1H), 5.12-5.15 (m, 1H), 5.28-5.31 (m, 1H), 5.40-5.44 (m, 1H), 6.10-6.16 (m, 1H), 7.31-7.33 (d, 1H), 7.79 (s, 2H). Analytical HPLC: 5.70 min. LC-MS ( $\text{ES}^+$ ): m/e = 494, 496 ( $\text{M}+\text{H}^+$ ).

15 4-Allyloxy-N-{2-[(2-benzyloxy-5-oxo-tetrahydro-furan-3-ylcarbamoyl)-methyl]-1-methanesulfonyl-3-oxo-[1,2]diazepan-4-yl}-3,5-dichloro-benzamide (26a) was prepared from [6-(4-allyloxy-3,5-dichloro-benzoylamino)-2-methanesulfonyl-7-oxo-[1,2]diazepan-1-yl]-acetic acid (25) and (2-benzyloxy-5-oxo-tetrahydro-furan-3-yl)-carbamic acid allyl ester (9, a mixture of diastereomers) by the method and chromatography used to prepare 10a to afford 178 mg (74% yield) of the title compound as a mixture of diastereomers.  $^1\text{H-NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.58-1.70 (m, 2H), 1.89-1.97 (m, 1H), 2.20-2.32 (m, 2H), 2.40-2.60 (m, 1H), 2.86-3.05 (m, 1H), 3.28-3.40 (m, 4H), 4.05-4.15 (m, 2H), 4.30-4.37 (m, 1H), 4.42-4.48 (m, 0.5H), 4.60-4.66 (m, 3H), 4.66-4.71 (m, 0.5H), 4.78-4.88 (m, 1H), 5.05-5.15 (m, 1H), 5.28-5.31 (d, 1H), 5.40-5.44 (m, 1H), 6.07-6.18 (m, 1H), 6.75-7.15 (m, 1H), 7.25-7.38 (m, 3H), 7.43-7.49 (m, 1H), 7.52-7.58 (m, 0.5H), 7.65-7.70 (m, 2H), 7.78 (s, 0.5H). Analytical HPLC (cyano column): 7.12 min. LC-MS ( $\text{ES}^+$ ): m/e = 683, 685 ( $\text{M}+\text{H}^+$ ).

Preparation of N-{2-[(2-Benzyl-5-oxo-tetrahydro-furan-3-ylcarbamoyl)-methyl]-1-methanesulfonyl-3-oxo-

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[1,2]diazepan-4-yl}-3,5-dichloro-4-hydroxy-benzamide (26b). 4-Allyloxy-N-{2-[(2-benzyloxy-5-oxo-tetrahydro-furan-3-ylcarbamoyl)-methyl]-1-methanesulfonyl-3-oxo-[1,2]diazepan-4-yl}-3,5-dichloro-benzamide (26a) (178 mg, 0.26 mmol) in dichloromethane (6 mL) was treated with DMBA (45 mg, 0.29 mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (20 mg, 0.017 mmol) at room temperature for 16 hours. The mixture was diluted with dichloromethane (40 mL), washed with water three times. The organic layer was dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and evaporated to give a pale yellow solid, that was purified by flash chromatography using dichloromethane/methanol (99.2/0.8 to 97.5/2.5) to afford 78 mg (47% yield) of *syn* diastereomer (higher R<sub>f</sub>) of the title compound and 59 mg (35% yield) of *anti* diastereomer (lower R<sub>f</sub>). <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>) for the *syn* diastereomer: δ 1.60-1.70 (m, 1H), 1.88-1.91 (m, 1H), 2.22-2.32 (m, 2H), 2.48-2.58 (m, 1H), 2.84-2.90 (m, 1H), 3.00 (s, 3H), 3.27-3.40 (m, 1H), 4.05-4.18 (m, 2H), 4.22-4.35 (m, 1H), 4.55-4.80 (m, 2H), 4.86-4.89 (d, 1H), 5.10-5.15 (m, 1H), 5.59-5.61 (d, 1H), 6.75-6.77 (d, 1H), 7.05-7.07 (d, 1H), 7.25-7.37 (m, 5H), 7.70 (s, 2H); and for the *anti* diastereomer: δ 1.60-1.80 (m, 1H), 1.85-1.95 (m, 1H), 2.20-2.39 (m, 2H), 2.39-2.50 (m, 1H), 3.00-3.10 (m, 1H), 3.12 (s, 3H), 3.28-3.42 (m, 1H), 4.05-4.15 (m, 2H), 4.28-4.47 (m, 2H), 4.56-4.62 (m, 1H), 4.77-4.83 (d, 1H), 5.10-5.20 (m, 1H), 5.43 (s, 1H), 6.93-6.94 (d, 1H), 7.09-7.11 (d, 1H), 7.25-7.39 (m, 5H), 7.80 (s, 2H). Analytical HPLC: 11.13 and 11.36 min. LC-MS (ES<sup>+</sup>) for the mixture of diastereomers: m/e = 643, 645 (M+H<sup>+</sup>).

Preparation of 3-{2-[6-(3,5-Dichloro-4-hydroxy-benzoylamino)-2-methanesulfonyl-7-oxo-[1,2]diazepan-1-yl]-acetyl amino}-4-oxo-butyric acid (27). N-{2-[(2-Benzyl oxy-5-oxo-tetrahydro-furan-3-ylcarbamoyl)-methyl]-1-methanesulfonyl-3-oxo-[1,2]diazepan-4-yl}-3,5-dichloro-4-hydroxy-benzamide (26b) was stirred in CH<sub>3</sub>CN (0.5 mL)

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and 2N HCl (1 mL) for 7 hours. The solution was concentrated in vacuo to half of the volume and extracted with ether (2 mL x 4). The combined ether layers was diluted with ethyl acetate/hexane (1/9, 3 mL), washed 5 with 1M Na<sub>2</sub>CO<sub>3</sub> (2 mL). The aqueous solution was washed with ethyl acetate/hexane (1/9, 2 mL x 2), acidified with 6N HCl to pH ~ 3, extracted with ethyl acetate (1.5 mL x 3). The combined extracts were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to dryness in vacuo to 10 afford 20 mg (47% yield) of the title compound. <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub> + CD<sub>3</sub>OD) δ 0.75-0.90 (m, 1H), 1.18-1.30 (m, 3H), 1.67-1.88 (m, 1H), 1.93-2.30 (m, 2H), 2.40-2.61 (m, 1H), 3.10-3.16 (m, 3H), 3.95-4.30 (m, 2H), 4.30-4.50 (m, 1H), 5.00-5.08 (d, 1H), 7.81 (s, 2H). Analytical 15 HPLC: 8.10 min. LC-MS (ES<sup>+</sup>): m/e = 553, 555 (M+H<sup>+</sup>) ..

\*Analytical HPLC conditions:

Column: Microsorb<sup>TM</sup> C-18, 5μ, 4.6 x 150 mm (unless noted).

20 Solvent A: 0.1% TFA / 1% MeCN / 98.9% water

Solvent B: 0.1% TFA / 99.9% MeCN

Gradient: A to B over 20 min at a flow rate of 1 mL/min

Example 8

Table 1. In Vitro Data

5

Cmp	ICE Caspase-1 Ki (nM)	CPP32 Caspase-3 Ki (nM)	Flice Caspase-8 Ki (nM)	PBMC IC50 (nM)	Whole Blood IC50 (nM)
<b>11a</b>	101			1400	7300
<b>11b</b>	120			1500	5800
<b>11c</b>	16	22200	1500	420	1450
<b>20</b>	0.9			540	830
<b>27</b>	17			1000	1900

Insofar as the compounds of this invention are able to inhibit caspases, particularly ICE, in vitro and furthermore, may be delivered orally to mammals, they are

10 of evident clinical utility for the treatment of IL-1-, apoptosis-, IGIF-, and IFN- $\gamma$ -mediated diseases.

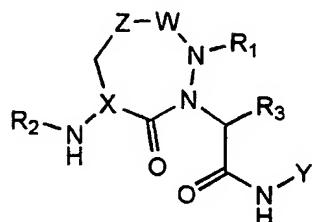
While we have described a number of embodiments of this invention, it is apparent that our basic constructions may be altered to provide other embodiments 15 which utilize the products and processes of this invention.

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Claims

What is claimed is:

1. A compound represented by formula (I):

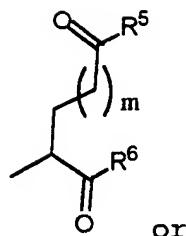


5

wherein:

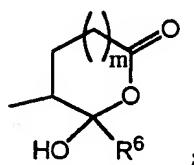
Y is:

(a)



10

(b)



m is 0 or 1;

15

W is -CH2-, -C(O)-, S(O)2, or -S(O)-;

X is -C(H)-, -C(R8)-, or -N-;

20

Z is -CH2-, -O-, -S-, or -N(R1)-, provided that if Z is -N(R1)-, then W is -C(O)-, -S(O)2-, or -S(O)-;

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each R<sup>1</sup> is independently -H, -C(O)R<sup>8</sup>, -S(O)<sub>2</sub>R<sup>8</sup>, -S(O)R<sup>8</sup>, -R<sup>21</sup>, -alkyl-R<sup>21</sup>, -alkenyl-R<sup>21</sup>, -alkynyl-R<sup>21</sup>, -alkyl;

5           R<sup>2</sup> is -C(O)R<sup>8</sup>, -C(O)C(O)R<sup>8</sup>, -S(O)<sub>2</sub>R<sup>8</sup>, -S(O)R<sup>8</sup>, -C(O)OR<sup>8</sup>, -C(O)N(H)R<sup>8</sup>, -S(O)<sub>2</sub>N(H)-R<sup>8</sup>, -S(O)N(H)-R<sup>8</sup>, -C(O)C(O)N(H)R<sup>8</sup>, -C(O)CH=CHR<sup>8</sup>, -C(O)CH<sub>2</sub>OR<sup>8</sup>, -C(O)CH<sub>2</sub>N(H)R<sup>8</sup>, -C(O)N(R<sup>8</sup>)<sub>2</sub>, -S(O)<sub>2</sub>N(R<sup>8</sup>)<sub>2</sub>, -S(O)N(R<sup>8</sup>)<sub>2</sub>, -C(O)C(O)N(R<sup>8</sup>)<sub>2</sub>, -C(O)CH<sub>2</sub>N(R<sup>8</sup>)<sub>2</sub>, -CH<sub>2</sub>-R<sup>8</sup>,  
10       -CH<sub>2</sub>-alkenyl-R<sup>8</sup>, or -CH<sub>2</sub>-alkynyl-R<sup>8</sup>;

R<sup>3</sup> is -H, -R<sup>21</sup>, -alkyl-R<sup>21</sup>, -alkenyl-R<sup>21</sup>, -alkynyl-R<sup>21</sup>, alkyl, or an amino acid side chain;

15           each R<sup>4</sup> is independently -OH, -F, -Cl, -Br, -I, -NO<sub>2</sub>, -CN, -NH<sub>2</sub>, -CO<sub>2</sub>H, -C(O)NH<sub>2</sub>, -N(H)C(O)H, -N(H)C(O)NH<sub>2</sub>, -alkyl, -cycloalkyl, -perfluoroalkyl, -O-alkyl, -N(H)alkyl, -N(alkyl)<sub>2</sub>, -C(O)N(H)alkyl, -C(O)N(alkyl)<sub>2</sub>, -N(H)C(O)alkyl, -N(H)C(O)N(H)alkyl,  
20       -N(H)C(O)N(alkyl)<sub>2</sub>, -S-alkyl, -S(O)<sub>2</sub>alkyl, -S(O)alkyl, -C(O)alkyl, -CH<sub>2</sub>NH<sub>2</sub>, -CH<sub>2</sub>N(H)alkyl, -CH<sub>2</sub>N(alkyl)<sub>2</sub>, or -N(H)C(O)Oalkyl;

25           R<sup>5</sup> is -OH, -OR<sup>8</sup>, -N(H)OH, or -N(H)SO<sub>2</sub>R<sup>8</sup>;

R<sup>6</sup> is -H, -CH<sub>2</sub>OR<sup>9</sup>, -CH<sub>2</sub>SR<sup>10</sup>, -CH<sub>2</sub>N(H)R<sup>9</sup>, -CH<sub>2</sub>N(R<sup>9</sup>)R<sup>11</sup>, -C(H)N<sub>2</sub>, -CH<sub>2</sub>F, -CH<sub>2</sub>Cl, -CH<sub>2</sub>Br, -CH<sub>2</sub>I, -C(O)N(R<sup>11</sup>)<sub>2</sub>, -R<sup>13</sup>, or -R<sup>14</sup>;

30           each R<sup>8</sup> is independently -alkyl, -cycloalkyl, -aryl, -heteroaryl, -heterocyclyl, -alkylcycloalkyl, -alkylaryl, -alkylheteroaryl, or -alkylheterocyclyl;

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R<sup>9</sup> is -H, -C(O)aryl, -C(O)heteroaryl,  
 -C(O)alkylaryl, -C(O)alkylheteroaryl, -alkylaryl,  
 -alkylheteroaryl, -aryl, -heteroaryl, or -P(O)(R<sup>15</sup>)<sub>2</sub>;

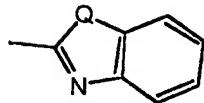
5            R<sup>10</sup> is -alkylaryl or -alkylheteroaryl;

each R<sup>11</sup> is independently -H, -alkyl, -aryl,  
 -heteroaryl, -cycloalkyl, -alkylaryl, or  
 -alkylheteroaryl;

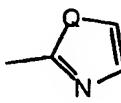
10

R<sup>13</sup> is -alkylaryl or -alkylheteroaryl;

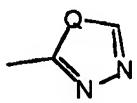
R<sup>14</sup> is



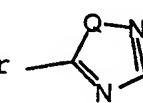
(i)



(ii)



(iii)



(iv)

wherein Q is -O- or -S-, any hydrogen atom in (i) is optionally replaced with -R<sup>17</sup>, and any hydrogen atom in (ii), (iii), and (iv) is optionally replaced with -R<sup>17</sup>, -R<sup>18</sup> or -alkyl-R<sup>18</sup>;

20

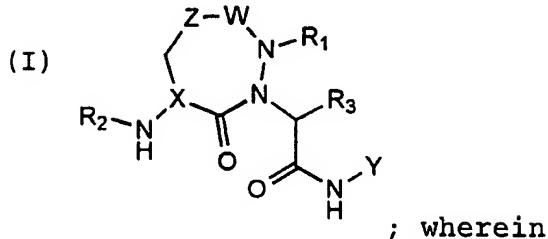
each R<sup>15</sup> is independently -H, -OH, -alkyl,  
 -aryl, -heteroaryl, -cycloalkyl, -alkylaryl,  
 -alkylheteroaryl, -Oalkyl, -Oaryl, -Oheteroaryl,  
 -Oalkylaryl, or -Oalkylheteroaryl;

25

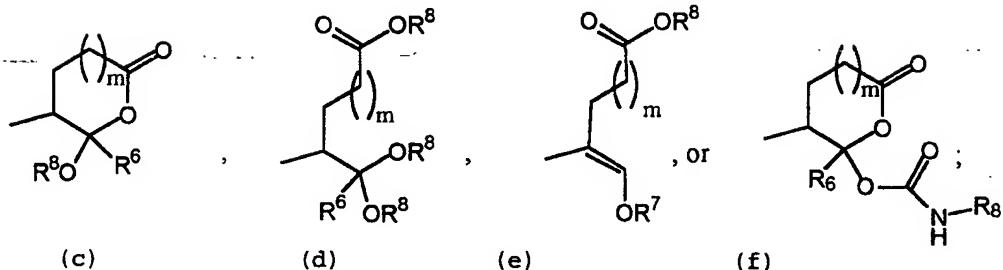
each R<sup>17</sup> is independently -OH, -F, -Cl, -Br,  
 -I, -NO<sub>2</sub>, -CN, -NH<sub>2</sub>, -CO<sub>2</sub>H, -C(O)NH<sub>2</sub>, -N(H)C(O)H,  
 -N(H)C(O)NH<sub>2</sub>, -SO<sub>2</sub>NH<sub>2</sub>, -C(O)H, -alkyl, -cycloalkyl,  
 -perfluoroalkyl, -O-alkyl, -N(H)alkyl, -N(alkyl)<sub>2</sub>,  
 -CO<sub>2</sub>alkyl, -C(O)N(H)alkyl, -C(O)N(alkyl)<sub>2</sub>,  
 -N(H)C(O)alkyl, -N(H)C(O)N(H)alkyl, -N(H)C(O)N(alkyl)<sub>2</sub>,  
 -S(O)<sub>2</sub>N(H)alkyl, -S(O)N(H)alkyl, -S(O)<sub>2</sub>N(alkyl)<sub>2</sub>,  
 -S(O)N(alkyl)<sub>2</sub>, -S-alkyl, -S(O)<sub>2</sub>alkyl, -S(O)alkyl, or  
 -C(O)alkyl;

each R<sup>18</sup> is independently -aryl, -heteroaryl,  
-alkylaryl, -alkylheteroaryl, -O-aryl, -O-heteroaryl,  
-O-alkylaryl, -O-alkylheteroaryl, -N(H)aryl, -N(aryl)<sub>2</sub>,  
5 -N(H)heteroaryl, -N(heteroaryl)<sub>2</sub>, -N(H)alkylaryl,  
-N(alkylaryl)<sub>2</sub>, -N(H)alkylheteroaryl,  
-N(alkylheteroaryl)<sub>2</sub>, -S-aryl, -S-heteroaryl,  
-S-alkylaryl, -S-alkylheteroaryl, -C(O)aryl,  
-C(O)heteroaryl, -C(O)alkylaryl, -C(O)alkylheteroaryl,  
10 -CO<sub>2</sub>aryl, -CO<sub>2</sub>heteroaryl, -CO<sub>2</sub>alkylaryl,  
-CO<sub>2</sub>alkylheteroaryl, -C(O)N(H)aryl, -C(O)N(aryl)<sub>2</sub>,  
-C(O)N(H)heteroaryl, -C(O)N(heteroaryl)<sub>2</sub>,  
-C(O)N(H)alkylaryl, -C(O)N(alkylaryl)<sub>2</sub>,  
-C(O)N(H)alkylheteroaryl, -C(O)N(alkylheteroaryl)<sub>2</sub>,  
15 -S(O)<sub>2</sub>-aryl, -S(O)-aryl, -S(O)<sub>2</sub>-heteroaryl,  
-S(O)-heteroaryl, -S(O)<sub>2</sub>-alkylaryl, -S(O)-alkylaryl,  
-S(O)<sub>2</sub>-alkylheteroaryl, -S(O)-alkylheteroaryl,  
-S(O)<sub>2</sub>N(H)-aryl, -S(O)N(H)-aryl, -S(O)<sub>2</sub>NH-heteroaryl,  
-S(O)NH-heteroaryl, -S(O)<sub>2</sub>N(H)-alkylaryl,  
20 -S(O)N(H)-alkylaryl, -S(O)<sub>2</sub>N(H)-alkylheteroaryl,  
-S(O)N(H)-alkylheteroaryl, -S(O)<sub>2</sub>N(aryl)<sub>2</sub>, -S(O)N(aryl)<sub>2</sub>,  
-S(O)<sub>2</sub>N(heteroaryl)<sub>2</sub>, -S(O)N(heteroaryl)<sub>2</sub>,  
-S(O)<sub>2</sub>N(alkylaryl)<sub>2</sub>, -S(O)N(alkylaryl)<sub>2</sub>,  
-S(O)<sub>2</sub>N(alkylheteroaryl)<sub>2</sub>, -S(O)N(alkylheteroaryl)<sub>2</sub>,  
25 -N(H)C(O)N(H)aryl, -N(H)C(O)N(H)heteroaryl,  
-N(H)C(O)N(H)alkylaryl, -N(H)C(O)N(H)alkylheteroaryl,  
-N(H)C(O)N(aryl)<sub>2</sub>, -N(H)C(O)N(heteroaryl)<sub>2</sub>,  
-N(H)C(O)N(alkylaryl)<sub>2</sub>, or -N(H)C(O)N(alkylheteroaryl)<sub>2</sub>;  
and  
30 each R<sup>21</sup> is independently -aryl, -heteroaryl,  
cycloalkyl, or -heterocyclyl, wherein a hydrogen atom  
bound to any carbon atom is optionally replaced by R<sup>4</sup> and  
35 a hydrogen atom bound to any nitrogen atom is optionally  
replaced by R<sup>2</sup>.

2. A compound represented by formula (I):



5 Y is:



m is 0 or 1;

10 W is  $\text{-CH}_2\text{-}$ ,  $\text{-C(O)-}$ ,  $\text{S(O)}_2$ , or  $\text{-S(O)-}$ ;

X is -C(H)-, -C(R<sup>8</sup>)-, or -N-;

15                    Z is  $\text{-CH}_2\text{-}$ ,  $\text{-O-}$ ,  $\text{-S-}$ , or  $\text{-N(R}^1\text{)-}$ , provided that if Z is  $\text{-N(R}^1\text{)-}$ , then W is  $\text{-C(O)-}$ ,  $\text{-S(O)---}$ , or  $\text{-S(O)-}$ :

each R<sup>1</sup> is independently -H, -C(O)R<sup>8</sup>, -S(O)<sub>2</sub>R<sup>8</sup>,  
 20 -S(O)R<sup>8</sup>, -R<sup>21</sup>, -alkyl-R<sup>21</sup>, -alkenyl-R<sup>21</sup>, -alkynyl-R<sup>21</sup>,  
 -alkyl;

R<sup>2</sup> is -C(O)R<sup>8</sup>, -C(O)C(O)R<sup>8</sup>, -S(O)<sub>2</sub>R<sup>8</sup>, -S(O)R<sup>8</sup>,  
 -C(O)OR<sup>8</sup>, -C(O)N(H)R<sup>8</sup>, -S(O)<sub>2</sub>N(H)-R<sup>8</sup>, -S(O)N(H)-R<sup>8</sup>,  
 25 -C(O)C(O)N(H)R<sup>8</sup>, -C(O)CH=CHR<sup>8</sup>, -C(O)CH<sub>2</sub>OR<sup>8</sup>,

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-C(O)CH<sub>2</sub>N(H)R<sup>8</sup>, -C(O)N(R<sup>8</sup>)<sub>2</sub>, -S(O)<sub>2</sub>N(R<sup>8</sup>)<sub>2</sub>, -S(O)N(R<sup>8</sup>)<sub>2</sub>,  
 -C(O)C(O)N(R<sup>8</sup>)<sub>2</sub>, -C(O)CH<sub>2</sub>N(R<sup>8</sup>)<sub>2</sub>, -CH<sub>2</sub>-R<sup>8</sup>,  
 -CH<sub>2</sub>-alkenyl-R<sup>8</sup>, or -CH<sub>2</sub>-alkynyl-R<sup>8</sup>;

5 R<sup>3</sup> is -H, -R<sup>21</sup>, -alkyl-R<sup>21</sup>, -alkenyl-R<sup>21</sup>,  
 -alkynyl-R<sup>21</sup>, alkyl, or an amino acid side chain;

each R<sup>4</sup> is independently -OH, -F, -Cl, -Br, -I,  
 -NO<sub>2</sub>, -CN, -NH<sub>2</sub>, -CO<sub>2</sub>H, -C(O)NH<sub>2</sub>, -N(H)C(O)H,  
 10 -N(H)C(O)NH<sub>2</sub>, -alkyl, -cycloalkyl, -perfluoroalkyl,  
 -O-alkyl, -N(H)alkyl, -N(alkyl)<sub>2</sub>, -C(O)N(H)alkyl,  
 -C(O)N(alkyl)<sub>2</sub>, -N(H)C(O)alkyl, -N(H)C(O)N(H)alkyl,  
 -N(H)C(O)N(alkyl)<sub>2</sub>, -S-alkyl, -S(O)<sub>2</sub>alkyl, -S(O)alkyl,  
 -C(O)alkyl, -CH<sub>2</sub>NH<sub>2</sub>, -CH<sub>2</sub>N(H)alkyl, -CH<sub>2</sub>N(alkyl)<sub>2</sub>, or  
 15 -N(H)C(O)Oalkyl;

R<sup>6</sup> is -H, -CH<sub>2</sub>OR<sup>9</sup>, -CH<sub>2</sub>SR<sup>10</sup>, -CH<sub>2</sub>N(H)R<sup>9</sup>,  
 -CH<sub>2</sub>N(R<sup>9</sup>)R<sup>11</sup>, -C(H)N<sub>2</sub>, -CH<sub>2</sub>F, -CH<sub>2</sub>Cl, -CH<sub>2</sub>Br, -CH<sub>2</sub>I,  
 -C(O)N(R<sup>11</sup>)<sub>2</sub>, -R<sup>13</sup>, or -R<sup>14</sup>;

20 R<sup>7</sup> is -C(O)alkyl, -C(O)cycloalkyl,  
 -C(O)alkylenyl, -C(O)alkylaryl, -C(O)alkylheteroaryl,  
 -C(O)heterocycle, or -C(O)alkylheterocycle;

25 each R<sup>8</sup> is independently -alkyl, -cycloalkyl,  
 -aryl, -heteroaryl, -heterocyclyl, -alkylcycloalkyl  
 -alkylaryl, -alkylheteroaryl, or -alkylheterocyclyl;

30 R<sup>9</sup> is -H, -C(O)aryl, -C(O)heteroaryl,  
 -C(O)alkylaryl, -C(O)alkylheteroaryl, -alkylaryl,  
 -alkylheteroaryl, -aryl, -heteroaryl, or -P(O)(R<sup>15</sup>)<sub>2</sub>;

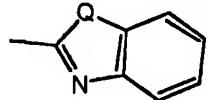
R<sup>10</sup> is -alkylaryl or -alkylheteroaryl;

- 100 -

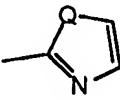
each R<sup>11</sup> is independently -H, -alkyl, -aryl, -heteroaryl, -cycloalkyl, -alkylaryl, or -alkylheteroaryl;

5                   R<sup>13</sup> is -alkylaryl or -alkylheteroaryl;

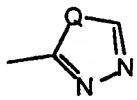
R<sup>14</sup> is



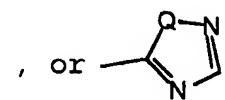
(i)



(ii)



(iii)



(iv)

10                  wherein Q is -O- or -S-, any hydrogen atom in (i) is optionally replaced with -R<sup>17</sup>, and any hydrogen atom in (ii), (iii), and (iv) is optionally replaced with -R<sup>17</sup>, -R<sup>18</sup> or -alkyl-R<sup>18</sup>;

15                  each R<sup>15</sup> is independently -H, -OH, -alkyl, -aryl, -heteroaryl, -cycloalkyl, -alkylaryl, -alkylheteroaryl, -Oalkyl, -Oaryl, -Oheteroaryl, -Oalkylaryl, or -Oalkylheteroaryl;

20                  each R<sup>17</sup> is independently -OH, -F, -Cl, -Br, -I, -NO<sub>2</sub>, -CN, -NH<sub>2</sub>, -CO<sub>2</sub>H, -C(O)NH<sub>2</sub>, -N(H)C(O)H, -N(H)C(O)NH<sub>2</sub>, -SO<sub>2</sub>NH<sub>2</sub>, -C(O)H, -alkyl, -cycloalkyl, -perfluoroalkyl, -O-alkyl, -N(H)alkyl, -N(alkyl)<sub>2</sub>, -CO<sub>2</sub>alkyl, -C(O)N(H)alkyl, -C(O)N(alkyl)<sub>2</sub>,

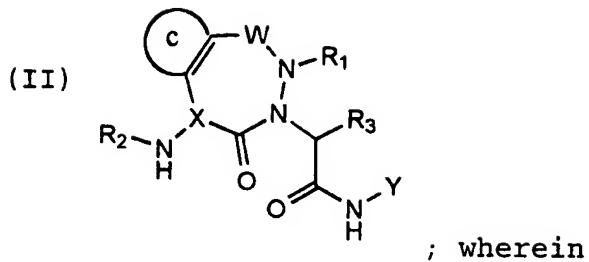
25                  -N(H)C(O)alkyl, -N(H)C(O)N(H)alkyl, -N(H)C(O)N(alkyl)<sub>2</sub>, -S(O)<sub>2</sub>N(H)alkyl, -S(O)N(H)alkyl, -S(O)<sub>2</sub>N(alkyl)<sub>2</sub>, -S(O)N(alkyl)<sub>2</sub>, -S-alkyl, -S(O)<sub>2</sub>alkyl, -S(O)alkyl, or -C(O)alkyl;

30                  each R<sup>18</sup> is independently -aryl, -heteroaryl, -alkylaryl, -alkylheteroaryl, -O-aryl, -O-heteroaryl, -O-alkylaryl, -O-alkylheteroaryl, -N(H)aryl, -N(aryl)<sub>2</sub>, -N(H)heteroaryl, -N(heteroaryl)<sub>2</sub>, -N(H)alkylaryl, -N(alkylaryl)<sub>2</sub>, -N(H)alkylheteroaryl,

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- N(alkylheteroaryl)<sub>2</sub>, -S-aryl, -S-heteroaryl,
  - S-alkylaryl, -S-alkylheteroaryl, -C(O)aryl,
  - C(O)heteroaryl, -C(O)alkylaryl, -C(O)alkylheteroaryl,
  - CO<sub>2</sub>aryl, -CO<sub>2</sub>heteroaryl, -CO<sub>2</sub>alkylaryl,
  - 5 -CO<sub>2</sub>alkylheteroaryl, -C(O)N(H)aryl, -C(O)N(aryl)<sub>2</sub>,
  - C(O)N(H)heteroaryl, -C(O)N(heteroaryl)<sub>2</sub>,
  - C(O)N(H)alkylaryl), -C(O)N(alkylaryl)<sub>2</sub>,
  - C(O)N(H)alkylheteroaryl, -C(O)N(alkylheteroaryl)<sub>2</sub>,
  - S(O)<sub>2</sub>-aryl, -S(O)-aryl, -S(O)<sub>2</sub>-heteroaryl,
  - 10 -S(O)-heteroaryl, -S(O)<sub>2</sub>-alkylaryl, -S(O)-alkylaryl,
  - S(O)<sub>2</sub>-alkylheteroaryl, -S(O)-alkylheteroaryl,
  - S(O)<sub>2</sub>N(H)-aryl, -S(O)N(H)-aryl, -S(O)<sub>2</sub>NH-heteroaryl,
  - S(O)NH-heteroaryl, -S(O)<sub>2</sub>N(H)-alkylaryl,
  - S(O)N(H)-alkylaryl, -S(O)<sub>2</sub>N(H)-alkylheteroaryl,
  - 15 -S(O)N(H)-alkylheteroaryl, -S(O)<sub>2</sub>N(aryl)<sub>2</sub>, -S(O)N(aryl)<sub>2</sub>,
  - S(O)<sub>2</sub>N(heteroaryl)<sub>2</sub>, -S(O)N(heteroaryl)<sub>2</sub>,
  - S(O)<sub>2</sub>N(alkylaryl)<sub>2</sub>, -S(O)N(alkylaryl)<sub>2</sub>,
  - S(O)<sub>2</sub>N(alkylheteroaryl)<sub>2</sub>, -S(O)N(alkylheteroaryl)<sub>2</sub>,
  - N(H)C(O)N(H)aryl, -N(H)C(O)N(H)heteroaryl,
  - 20 -N(H)C(O)N(H)alkylaryl, -N(H)C(O)N(H)alkylheteroaryl,
  - N(H)C(O)N(aryl)<sub>2</sub>, -N(H)C(O)N(heteroaryl)<sub>2</sub>,
  - N(H)C(O)N(alkylaryl)<sub>2</sub>, or -N(H)C(O)N(alkylheteroaryl)<sub>2</sub>;
  - and
  - 25 each R<sup>21</sup> is independently -aryl, -heteroaryl, cycloalkyl, or -heterocyclyl, wherein a hydrogen atom bound to any carbon atom is optionally replaced by R<sup>4</sup> and a hydrogen atom bound to any nitrogen atom is optionally replaced by R<sup>2</sup>.
  - 30
3. A compound represented by formula (II):

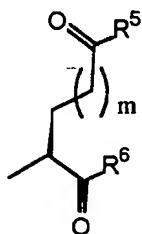
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Y is:

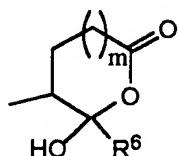
(a)

5



, or

(c)



10

C is an aryl or heteroaryl ring, wherein any hydrogen atom bound to the C ring is optionally substituted with -R<sup>4</sup>;

15

m is 0 or 1;

W is -CH<sub>2</sub>- , -C(O)- , S(O)<sub>2</sub> , or -S(O)- ;

20

X is -C(H)- , -C(R<sup>8</sup>)- , or -N- ;

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each R<sup>1</sup> is independently -H, -C(O)R<sup>8</sup>, -S(O)<sub>2</sub>R<sup>8</sup>, -S(O)R<sup>8</sup>, -R<sup>21</sup>, -alkyl-R<sup>21</sup>, -alkenyl-R<sup>21</sup>, -alkynyl-R<sup>21</sup>, -alkyl;

5           R<sup>2</sup> is -C(O)R<sup>8</sup>, -C(O)C(O)R<sup>8</sup>, -S(O)<sub>2</sub>R<sup>8</sup>, -S(O)R<sup>8</sup>, -C(O)OR<sup>8</sup>, -C(O)N(H)R<sup>8</sup>, -S(O)<sub>2</sub>N(H)-R<sup>8</sup>, -S(O)N(H)-R<sup>8</sup>, -C(O)C(O)N(H)R<sup>8</sup>, -C(O)CH=CHR<sup>8</sup>, -C(O)CH<sub>2</sub>OR<sup>8</sup>, -C(O)CH<sub>2</sub>N(H)R<sup>8</sup>, -C(O)N(R<sup>8</sup>)<sub>2</sub>, -S(O)<sub>2</sub>N(R<sup>8</sup>)<sub>2</sub>, -S(O)N(R<sup>8</sup>)<sub>2</sub>, -C(O)C(O)N(R<sup>8</sup>)<sub>2</sub>, -C(O)CH<sub>2</sub>N(R<sup>8</sup>)<sub>2</sub>, -CH<sub>2</sub>-R<sup>8</sup>,  
10        -CH<sub>2</sub>-alkenyl-R<sup>8</sup>, or -CH<sub>2</sub>-alkynyl-R<sup>8</sup>;

R<sup>3</sup> is -H, -R<sup>21</sup>, -alkyl-R<sup>21</sup>, -alkenyl-R<sup>21</sup>, -alkynyl-R<sup>21</sup>, alkyl, or an amino acid side chain;

15           each R<sup>4</sup> is independently -OH, -F, -Cl, -Br, -I, -NO<sub>2</sub>, -CN, -NH<sub>2</sub>, -CO<sub>2</sub>H, -C(O)NH<sub>2</sub>, -N(H)C(O)H, -N(H)C(O)NH<sub>2</sub>, -alkyl, -cycloalkyl, -perfluoroalkyl, -O-alkyl, -N(H)alkyl, -N(alkyl)<sub>2</sub>, -C(O)N(H)alkyl, -C(O)N(alkyl)<sub>2</sub>, -N(H)C(O)alkyl, -N(H)C(O)N(H)alkyl,  
20        -N(H)C(O)N(alkyl)<sub>2</sub>, -S-alkyl, -S(O)<sub>2</sub>alkyl, -S(O)alkyl, -C(O)alkyl, -CH<sub>2</sub>NH<sub>2</sub>, -CH<sub>2</sub>N(H)alkyl, -CH<sub>2</sub>N(alkyl)<sub>2</sub>, or -N(H)C(O)Oalkyl;

R<sup>5</sup> is -OH, -OR<sup>8</sup>, -N(H)OH, or -N(H)SO<sub>2</sub>R<sup>8</sup>;

25           R<sup>6</sup> is -H, -CH<sub>2</sub>OR<sup>9</sup>, -CH<sub>2</sub>SR<sup>10</sup>, -CH<sub>2</sub>N(H)R<sup>9</sup>, -CH<sub>2</sub>N(R<sup>9</sup>)R<sup>11</sup>, -C(H)N<sub>2</sub>, -CH<sub>2</sub>F, -CH<sub>2</sub>Cl, -CH<sub>2</sub>Br, -CH<sub>2</sub>I, -C(O)N(R<sup>11</sup>)<sub>2</sub>, -R<sup>13</sup>, or -R<sup>14</sup>;

30           each R<sup>8</sup> is independently -alkyl, -cycloalkyl, -aryl, -heteroaryl, -heterocyclyl, -alkylcycloalkyl, -alkylaryl, -alkylheteroaryl, or -alkylheterocyclyl;

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R<sup>9</sup> is -H, -C(O)aryl, -C(O)heteroaryl,  
 -C(O)alkylaryl, -C(O)alkylheteroaryl, -alkylaryl,  
 -alkylheteroaryl, -aryl, -heteroaryl, or -P(O)(R<sup>15</sup>)<sub>2</sub>;

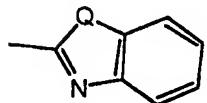
5 R<sup>10</sup> is -alkylaryl or -alkylheteroaryl;

each R<sup>11</sup> is independently -H, -alkyl, -aryl,  
 -heteroaryl, -cycloalkyl, -alkylaryl, or  
 -alkylheteroaryl;

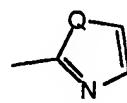
10

R<sup>13</sup> is -alkylaryl or alkylheteroaryl;

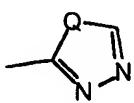
R<sup>14</sup> is



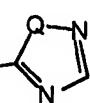
(i)



(ii)



(iii)



(iv)

wherein Q is -O- or -S-, any hydrogen atom in (i) is optionally replaced with -R<sup>17</sup>, and any hydrogen atom in (ii), (iii), and (iv) is optionally replaced with -R<sup>17</sup>, -R<sup>18</sup> or -alkyl-R<sup>18</sup>;

20

each R<sup>15</sup> is independently -H, -OH, -alkyl,  
 -aryl, -heteroaryl, -cycloalkyl, -alkylaryl,  
 -alkylheteroaryl, -Oalkyl, -Oaryl, -Oheteroaryl,  
 -Oalkylaryl, or -Oalkylheteroaryl;

25

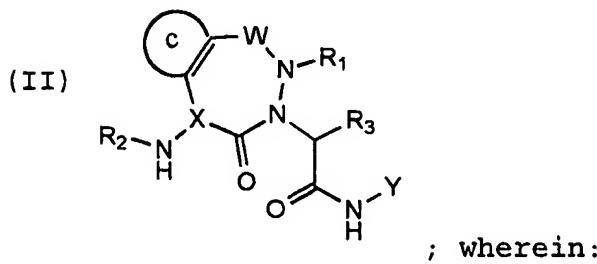
each R<sup>17</sup> is independently -OH, -F, -Cl, -Br,  
 -I, -NO<sub>2</sub>, -CN, -NH<sub>2</sub>, -CO<sub>2</sub>H, -C(O)NH<sub>2</sub>, -N(H)C(O)H,  
 -N(H)C(O)NH<sub>2</sub>, -SO<sub>2</sub>NH<sub>2</sub>, -C(O)H, -alkyl, -cycloalkyl,  
 -perfluoroalkyl, -O-alkyl, -N(H)alkyl, -N(alkyl)<sub>2</sub>,

30

-CO<sub>2</sub>alkyl, -C(O)N(H)alkyl, -C(O)N(alkyl)<sub>2</sub>,  
 -N(H)C(O)alkyl, -N(H)C(O)N(H)alkyl, -N(H)C(O)N(alkyl)<sub>2</sub>,  
 -S(O)<sub>2</sub>N(H)alkyl, -S(O)N(H)alkyl, -S(O)<sub>2</sub>N(alkyl)<sub>2</sub>,  
 -S(O)N(alkyl)<sub>2</sub>, -S-alkyl, -S(O)<sub>2</sub>alkyl, -S(O)alkyl, or  
 -C(O)alkyl;

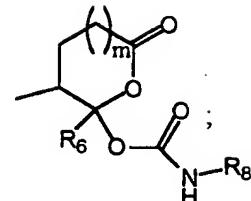
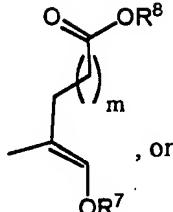
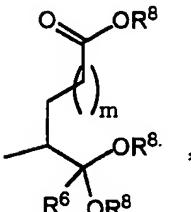
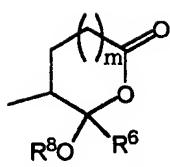
each R<sup>18</sup> is independently -aryl, -heteroaryl,  
-alkylaryl, -alkylheteroaryl, -O-aryl, -O-heteroaryl,  
-O-alkylaryl, -O-alkylheteroaryl, -N(H)aryl, -N(aryl)<sub>2</sub>,  
5 -N(H)heteroaryl, -N(heteroaryl)<sub>2</sub>, -N(H)alkylaryl,  
-N(alkylaryl)<sub>2</sub>, -N(H)alkylheteroaryl,  
-N(alkylheteroaryl)<sub>2</sub>, -S-aryl, -S-heteroaryl,  
-S-alkylaryl, -S-alkylheteroaryl, -C(O)aryl,  
-C(O)heteroaryl, -C(O)alkylaryl, -C(O)alkylheteroaryl,  
10 -CO<sub>2</sub>aryl, -CO<sub>2</sub>heteroaryl, -CO<sub>2</sub>alkylaryl,  
-CO<sub>2</sub>alkylheteroaryl, -C(O)N(H)aryl, -C(O)N(aryl)<sub>2</sub>,  
-C(O)N(H)heteroaryl, -C(O)N(heteroaryl)<sub>2</sub>,  
-C(O)N(H)alkylaryl, -C(O)N(alkylaryl)<sub>2</sub>,  
-C(O)N(H)alkylheteroaryl, -C(O)N(alkylheteroaryl)<sub>2</sub>,  
15 -S(O)<sub>2</sub>-aryl, -S(O)-aryl, -S(O)<sub>2</sub>-heteroaryl,  
-S(O)-heteroaryl, -S(O)<sub>2</sub>-alkylaryl, -S(O)-alkylaryl,  
-S(O)<sub>2</sub>-alkylheteroaryl, -S(O)-alkylheteroaryl,  
-S(O)<sub>2</sub>N(H)-aryl, -S(O)N(H)-aryl, -S(O)<sub>2</sub>NH-heteroaryl,  
-S(O)NH-heteroaryl, -S(O)<sub>2</sub>N(H)-alkylaryl,  
20 -S(O)N(H)-alkylaryl, -S(O)<sub>2</sub>N(H)-alkylheteroaryl,  
-S(O)N(H)-alkylheteroaryl, -S(O)<sub>2</sub>N(aryl)<sub>2</sub>, -S(O)N(aryl)<sub>2</sub>,  
-S(O)<sub>2</sub>N(heteroaryl)<sub>2</sub>, -S(O)N(heteroaryl)<sub>2</sub>,  
-S(O)<sub>2</sub>N(alkylaryl)<sub>2</sub>, -S(O)N(alkylaryl)<sub>2</sub>,  
-S(O)<sub>2</sub>N(alkylheteroaryl)<sub>2</sub>, -S(O)N(alkylheteroaryl)<sub>2</sub>,  
25 -N(H)C(O)N(H)aryl, -N(H)C(O)N(H)heteroaryl,  
-N(H)C(O)N(H)alkylaryl, -N(H)C(O)N(H)alkylheteroaryl,  
-N(H)C(O)N(aryl)<sub>2</sub>, -N(H)C(O)N(heteroaryl)<sub>2</sub>,  
-N(H)C(O)N(alkylaryl)<sub>2</sub>, or -N(H)C(O)N(alkylheteroaryl)<sub>2</sub>;  
and  
30 each R<sup>21</sup> is independently -aryl, -heteroaryl,  
cycloalkyl, or -heterocyclyl, wherein a hydrogen atom  
bound to any carbon atom is optionally replaced by R<sup>4</sup> and  
a hydrogen atom bound to any nitrogen atom is optionally  
35 replaced by R<sup>2</sup>.

4. A compound represented by formula  
 (II) :



5

-Y is:



10

C is an aryl or heteroaryl ring, wherein any hydrogen atom bound to the C ring is optionally substituted with -R<sup>4</sup>;

15

m is 0 or 1;

W is -CH<sub>2</sub>-, -C(O)-, S(O)<sub>2</sub>, or -S(O)-;

20

X is -C(H)-, -C(R<sup>8</sup>)-, or -N-;

each R<sup>1</sup> is independently -H, -C(O)R<sup>8</sup>, -S(O)<sub>2</sub>R<sup>8</sup>, -S(O)R<sup>8</sup>, -R<sup>21</sup>, -alkyl-R<sup>21</sup>, -alkenyl-R<sup>21</sup>, -alkynyl-R<sup>21</sup>, -alkyl;

25

- 107 -

$R^2$  is  $-C(O)R^8$ ,  $-C(O)C(O)R^8$ ,  $-S(O)_2R^8$ ,  $-S(O)R^8$ ,  
 $-C(O)OR^8$ ,  $-C(O)N(H)R^8$ ,  $-S(O)_2N(H)-R^8$ ,  $-S(O)N(H)-R^8$ ,  
 $-C(O)C(O)N(H)R^8$ ,  $-C(O)CH=CHR^8$ ,  $-C(O)CH_2OR^8$ ,  
 $-C(O)CH_2N(H)R^8$ ,  $-C(O)N(R^8)_2$ ,  $-S(O)_2N(R^8)_2$ ,  $-S(O)N(R^8)_2$ ,  
5  $-C(O)C(O)N(R^8)_2$ ,  $-C(O)CH_2N(R^8)_2$ ,  $-CH_2-R^8$ ,  
 $-CH_2\text{-alkenyl-}R^8$ , or  $-CH_2\text{-alkynyl-}R^8$ ;

$R^3$  is  $-H$ ,  $-R^{21}$ ,  $\text{-alkyl-}R^{21}$ ,  $\text{-alkenyl-}R^{21}$ ,  
 $\text{-alkynyl-}R^{21}$ , alkyl, or an amino acid side chain;

10 each  $R^4$  is independently  $-OH$ ,  $-F$ ,  $-Cl$ ,  $-Br$ ,  $-I$ ,  
 $-NO_2$ ,  $-CN$ ,  $-NH_2$ ,  $-CO_2H$ ,  $-C(O)NH_2$ ,  $-N(H)C(O)H$ ,  
 $-N(H)C(O)NH_2$ , -alkyl, -cycloalkyl, -perfluoroalkyl,  
 $-O\text{-alkyl}$ ,  $-N(H)\text{alkyl}$ ,  $-N(alkyl)_2$ ,  $-C(O)N(H)\text{alkyl}$ ,  
15  $-C(O)N(alkyl)_2$ ,  $-N(H)C(O)\text{alkyl}$ ,  $-N(H)C(O)N(H)\text{alkyl}$ ,  
 $-N(H)C(O)N(alkyl)_2$ ,  $-S\text{-alkyl}$ ,  $-S(O)_2\text{alkyl}$ ,  $-S(O)\text{alkyl}$ ,  
 $-C(O)\text{alkyl}$ ,  $-CH_2NH_2$ ,  $-CH_2N(H)\text{alkyl}$ ,  $-CH_2N(alkyl)_2$ , or  
 $-N(H)C(O)\text{alkyl}$ ;

20  $R^6$  is  $-H$ ,  $-CH_2OR^9$ ,  $-CH_2SR^{10}$ ,  $-CH_2N(H)R^9$ ,  
 $-CH_2N(R^9)R^{11}$ ,  $-C(H)N_2$ ,  $-CH_2F$ ,  $-CH_2Cl$ ,  $-CH_2Br$ ,  $-CH_2I$ ,  
 $-C(O)N(R^{11})_2$ ,  $-R^{13}$ , or  $-R^{14}$ ;

25  $R^7$  is  $-C(O)\text{alkyl}$ ,  $-C(O)\text{cycloalkyl}$ ,  
 $-C(O)\text{alkylenyl}$ ,  $-C(O)\text{alkylaryl}$ ,  $-C(O)\text{alkylheteroaryl}$ ,  
 $-C(O)\text{heterocycle}$ , or  $-C(O)\text{alkylheterocycle}$ ;

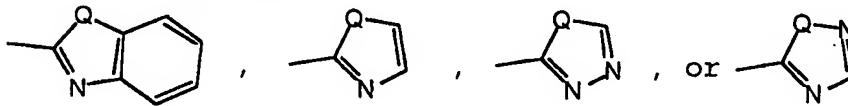
30 each  $R^8$  is independently -alkyl, -cycloalkyl,  
-aryl, -heteroaryl, -heterocyclyl, -alkylcycloalkyl  
 $-alkylaryl$ ,  $-alkylheteroaryl$ , or  $-alkylheterocyclyl$ ;

$R^9$  is  $-H$ ,  $-C(O)\text{aryl}$ ,  $-C(O)\text{heteroaryl}$ ,  
 $-C(O)\text{alkylaryl}$ ,  $-C(O)\text{alkylheteroaryl}$ ,  $-alkylaryl$ ,  
 $-alkylheteroaryl$ ,  $-aryl$ ,  $-heteroaryl$ , or  $-P(O)(R^{15})_2$ ;

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R<sup>10</sup> is -alkylaryl or -alkylheteroaryl;  
 each R<sup>11</sup> is independently -H, -alkyl, -aryl,  
 -heteroaryl, -cycloalkyl, -alkylaryl, or  
 5 -alkylheteroaryl;

R<sup>13</sup> is -alkylaryl or -alkylheteroaryl;

10 R<sup>14</sup> is  
  
 (i) (ii) (iii) (iv)

wherein Q is -O- or -S-, any hydrogen atom in (i)  
 is optionally replaced with -R<sup>17</sup>, and any hydrogen atom  
 in (ii), (iii), and (iv) is optionally replaced with  
 15 -R<sup>17</sup>, -R<sup>18</sup> or -alkyl-R<sup>18</sup>;

20 each R<sup>15</sup> is independently -H, -OH, -alkyl,  
 -aryl, -heteroaryl, -cycloalkyl, -alkylaryl,  
 -alkylheteroaryl, -Oalkyl, -Oaryl, -Oheteroaryl,  
 -Oalkylaryl, or -Oalkylheteroaryl;

each R<sup>17</sup> is independently -OH, -F, -Cl, -Br,  
 -I, -NO<sub>2</sub>, -CN, -NH<sub>2</sub>, -CO<sub>2</sub>H, -C(O)NH<sub>2</sub>, -N(H)C(O)H,  
 -N(H)C(O)NH<sub>2</sub>, -SO<sub>2</sub>NH<sub>2</sub>, -C(O)H, -alkyl, -cycloalkyl,  
 25 -perfluoroalkyl, -O-alkyl, -N(H)alkyl, -N(alkyl)<sub>2</sub>,  
 -CO<sub>2</sub>alkyl, -C(O)N(H)alkyl, -C(O)N(alkyl)<sub>2</sub>,  
 -N(H)C(O)alkyl, -N(H)C(O)N(H)alkyl, -N(H)C(O)N(alkyl)<sub>2</sub>,  
 -S(O)<sub>2</sub>N(H)alkyl, -S(O)N(H)alkyl, -S(O)<sub>2</sub>N(alkyl)<sub>2</sub>,  
 -S(O)N(alkyl)<sub>2</sub>, -S-alkyl, -S(O)<sub>2</sub>alkyl, -S(O)alkyl, or  
 30 -C(O)alkyl;

each R<sup>18</sup> is independently -aryl, -heteroaryl,  
 -alkylaryl, -alkylheteroaryl, -O-aryl, -O-heteroaryl,  
 -O-alkylaryl, -O-alkylheteroaryl, -N(H)aryl, -N(aryl)<sub>2</sub>,

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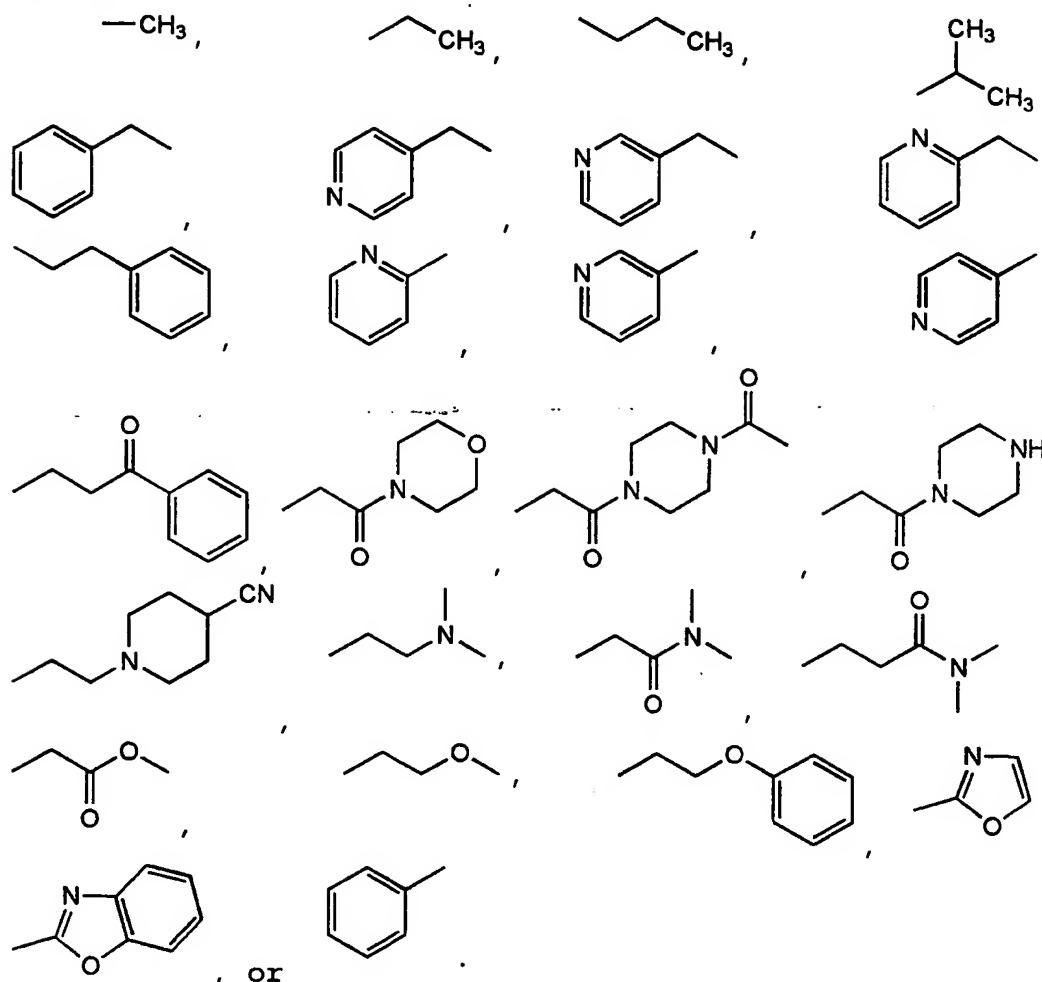
-N(H)heteroaryl, -N(heteroaryl)<sub>2</sub>, -N(H)alkylaryl,  
-N(alkylaryl)<sub>2</sub>, -N(H)alkylheteroaryl,  
-N(alkylheteroaryl)<sub>2</sub>, -S-aryl, -S-heteroaryl,  
-S-alkylaryl, -S-alkylheteroaryl, -C(O)aryl,  
5 -C(O)heteroaryl, -C(O)alkylaryl, -C(O)alkylheteroaryl,  
-CO<sub>2</sub>aryl, -CO<sub>2</sub>heteroaryl, -CO<sub>2</sub>alkylaryl,  
-CO<sub>2</sub>alkylheteroaryl, -C(O)N(H)aryl, -C(O)N(aryl)<sub>2</sub>,  
-C(O)N(H)heteroaryl, -C(O)N(heteroaryl)<sub>2</sub>,  
-C(O)N(H)alkylaryl, -C(O)N(alkylaryl)<sub>2</sub>,  
10 -C(O)N(H)alkylheteroaryl, -C(O)N(alkylheteroaryl)<sub>2</sub>,  
-S(O)<sub>2</sub>-aryl, -S(O)-aryl, -S(O)<sub>2</sub>-heteroaryl,  
-S(O)-heteroaryl, -S(O)<sub>2</sub>-alkylaryl, -S(O)-alkylaryl,  
-S(O)<sub>2</sub>-alkylheteroaryl, -S(O)-alkylheteroaryl,  
-S(O)<sub>2</sub>N(H)-aryl, -S(O)N(H)-aryl, -S(O)<sub>2</sub>NH-heteroaryl,  
15 -S(O)NH-heteroaryl, -S(O)<sub>2</sub>N(H)-alkylaryl,  
-S(O)N(H)-alkylaryl, -S(O)<sub>2</sub>N(H)-alkylheteroaryl,  
-S(O)N(H)-alkylheteroaryl, -S(O)<sub>2</sub>N(aryl)<sub>2</sub>, -S(O)N(aryl)<sub>2</sub>,  
-S(O)<sub>2</sub>N(heteroaryl)<sub>2</sub>, -S(O)N(heteroaryl)<sub>2</sub>,  
-S(O)<sub>2</sub>N(alkylaryl)<sub>2</sub>, -S(O)N(alkylaryl)<sub>2</sub>,  
20 -S(O)<sub>2</sub>N(alkylheteroaryl)<sub>2</sub>, -S(O)N(alkylheteroaryl)<sub>2</sub>,  
-N(H)C(O)N(H)aryl, -N(H)C(O)N(H)heteroaryl,  
-N(H)C(O)N(H)alkylaryl, -N(H)C(O)N(H)alkylheteroaryl,  
-N(H)C(O)N(aryl)<sub>2</sub>, -N(H)C(O)N(heteroaryl)<sub>2</sub>,  
-N(H)C(O)N(alkylaryl)<sub>2</sub>, or -N(H)C(O)N(alkylheteroaryl)<sub>2</sub>;  
25 and

each R<sup>21</sup> is independently -aryl, -heteroaryl,  
cycloalkyl, or -heterocyclyl, wherein a hydrogen atom  
bound to any carbon atom is optionally replaced by R<sup>4</sup> and  
30 a hydrogen atom bound to any nitrogen atom is optionally  
replaced by R<sup>2</sup>.

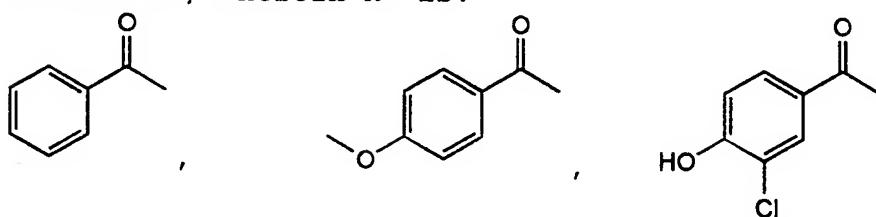
5. The compound according to any one of  
claims 1-4 wherein R<sup>1</sup> is aryl, heteroaryl, alkyl,  
35 alkylaryl, or alkylheteroaryl.

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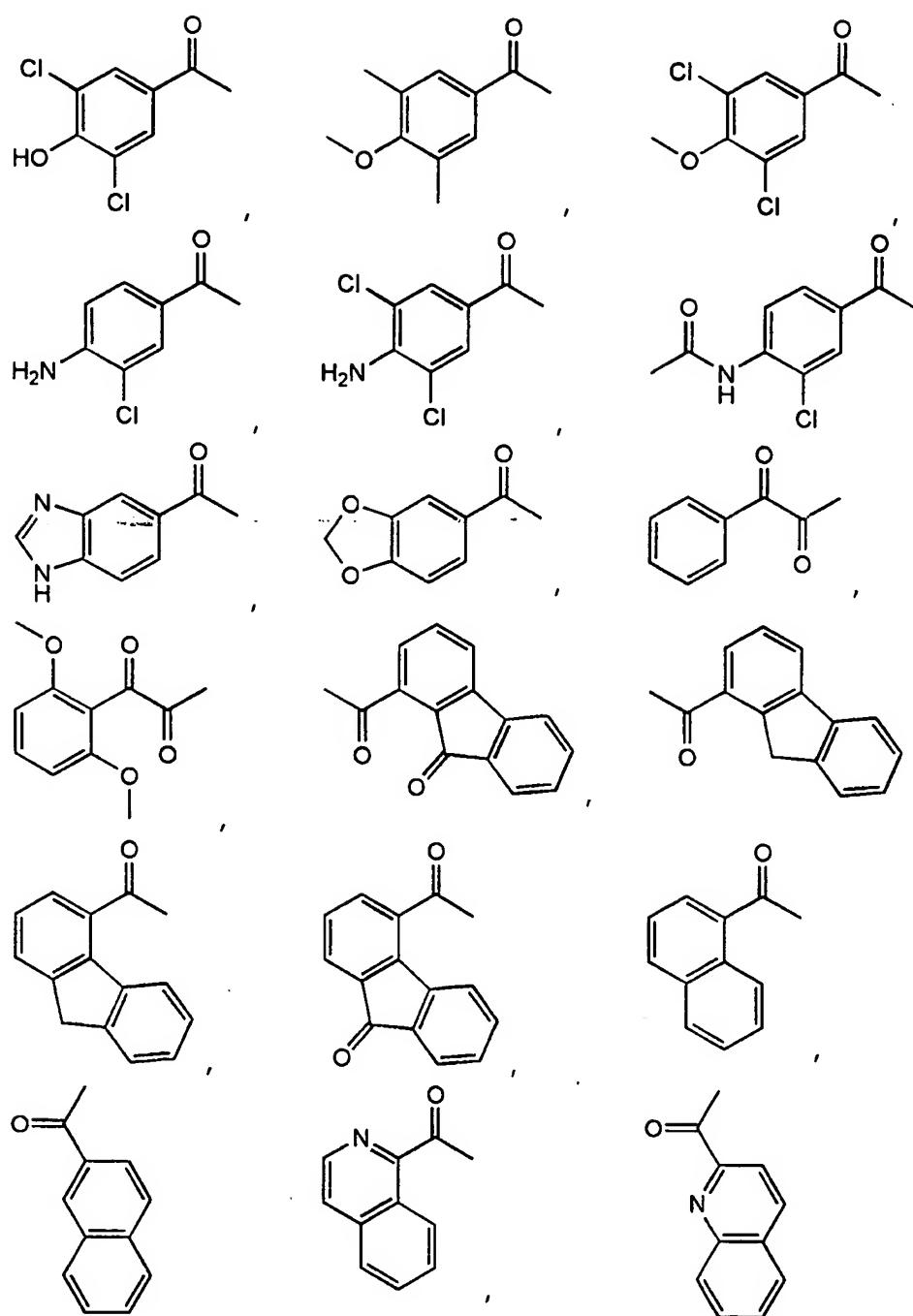
6. The compound according to claim 5, wherein

 $R^1$  is:

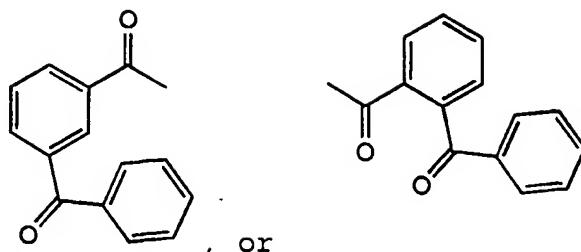
5

7. The compound according to any one of claims 1-4, wherein  $R^2$  is:

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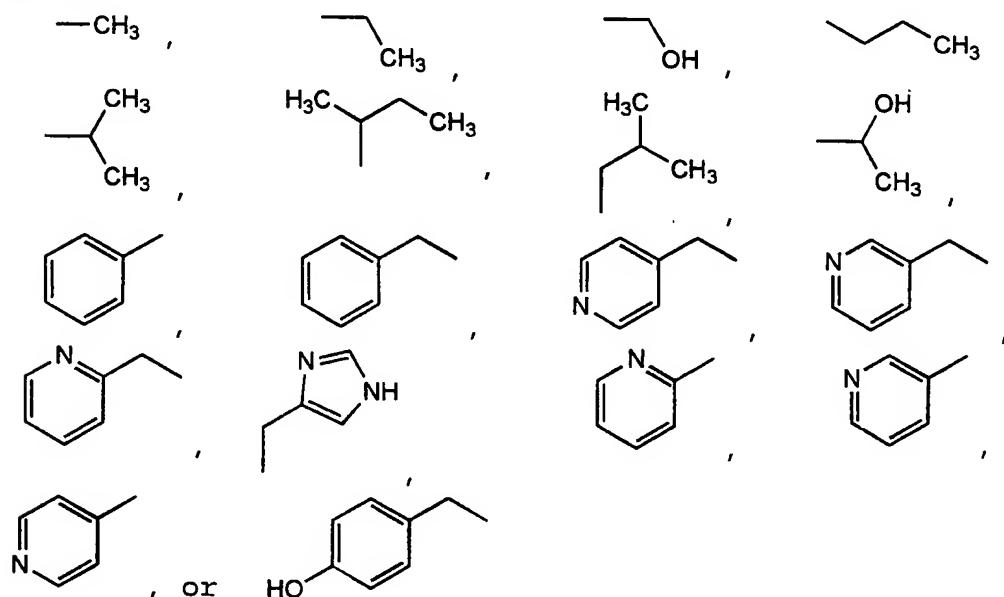


8. The compound according to any one of claims 1-4 wherein R<sup>3</sup> is an amino acid side chain, aryl, heteroaryl, alkyl, alkylaryl, or alkylheteroaryl.

5

9. The compound according to claim 8 wherein

$R^3$  is:



10. The compound according to any one of  
10 claims 1-4 wherein R<sup>6</sup> is -H.

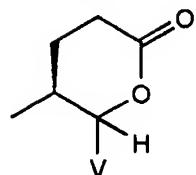
11. The compound according to claim 2 or  
claim 4 wherein -R<sup>8</sup> is -alkyl, -alkylcycloalkyl, -aryl,  
-alkylaryl, or alkylheterocyclyl,

15

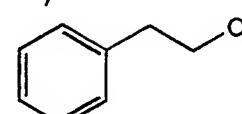
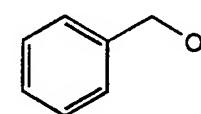
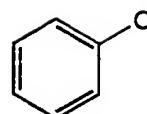
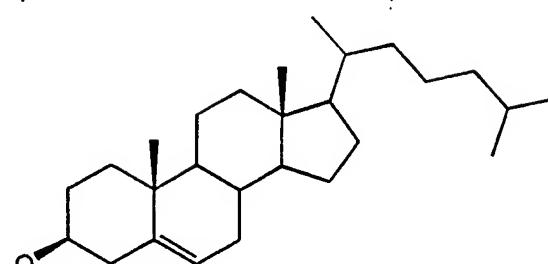
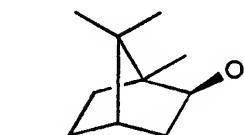
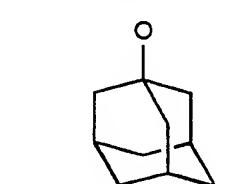
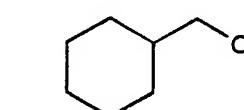
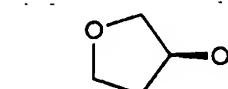
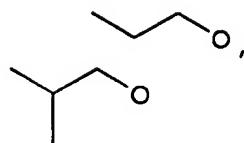
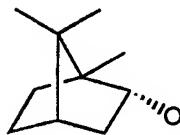
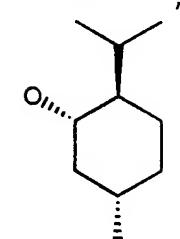
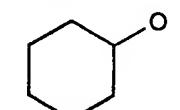
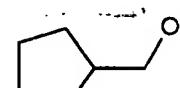
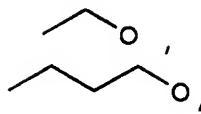
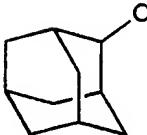
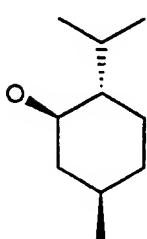
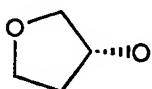
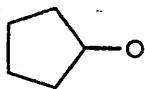
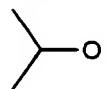
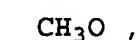
- 113 -

12. The compound according to claim 11,  
wherein Y is:

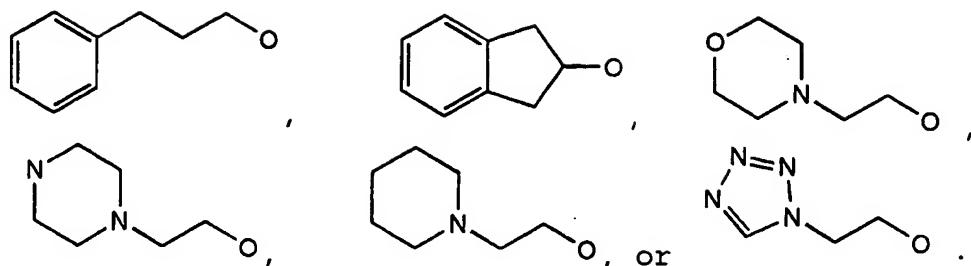
10



and V is:

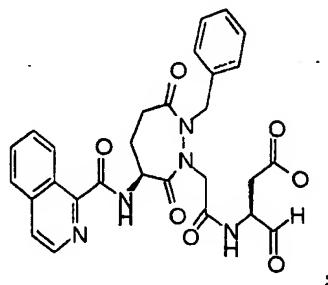


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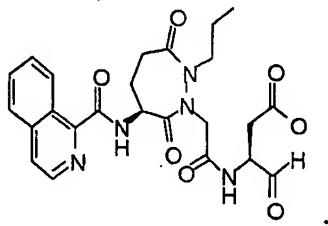


13. The compound according to claim 1 selected from the group consisting of:

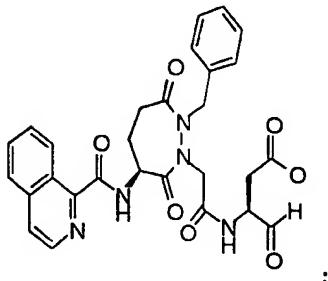
11a



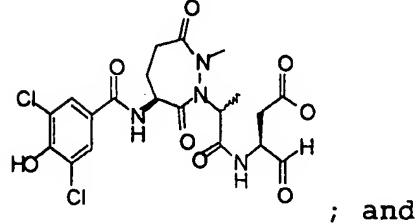
11b



11c



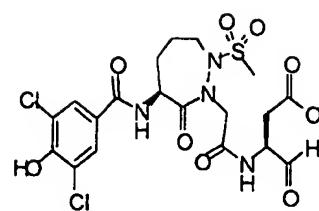
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; and

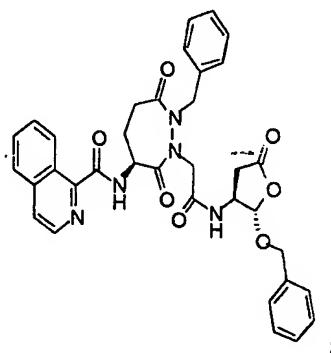
- 115 -

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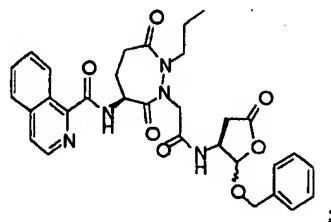


14. The compound according to claim 2 selected from the group consisting of:

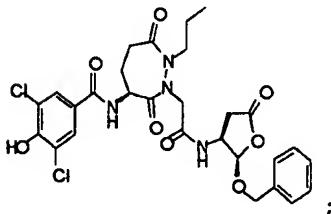
10a



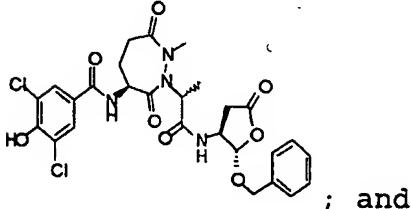
10b



10d



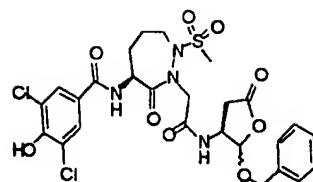
19



; and

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26b



15. A pharmaceutical composition comprising:

- a) a compound according to any one of claims 1-14; and b)  
5 a pharmaceutically acceptable carrier, adjuvant or vehicle.

16. A method for treating or preventing a disease selected from an IL-1 mediated disease, an  
10 apoptosis mediated disease, an inflammatory disease, an autoimmune disease, a destructive bone disorder, a proliferative disorder, an infectious disease, a degenerative disease, a necrotic disease, an excess dietary alcohol intake disease, a viral mediated disease,  
15 inflammatory peritonitis, osteoarthritis, pancreatitis, asthma, adult respiratory distress syndrome, glomerulonephritis, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Grave's disease, autoimmune gastritis, insulin-dependent diabetes  
20 mellitus (Type I), autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, chronic active hepatitis, myasthenia gravis, inflammatory bowel disease, Crohn's disease, psoriasis, graft vs host disease, osteoporosis, multiple myeloma-related bone  
25 disorder, acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, multiple myeloma, sepsis, septic shock, Shigellosis, Alzheimer's disease, Parkinson's disease, cerebral ischemia, myocardial ischemia, spinal muscular atrophy, multiple  
30 sclerosis, AIDS-related encephalitis, HIV-related encephalitis, aging, alopecia, neurological damage due to

stroke, ulcerative colitis, traumatic brain injury, organ transplant rejection, hepatitis-B, hepatitis-C, hepatitis-G, yellow fever, dengue fever, or Japanese encephalitis, in a patient comprising the step of  
5 administering to said patient a compound according to any one of claims 1-14 or a pharmaceutical composition according to claim 15.

10 17. The method according to claim 16, wherein the disease is rheumatoid arthritis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, inflammatory peritonitis, septic shock, pancreatitis, traumatic brain injury, organ transplant rejection, osteoarthritis, asthma, psoriasis, or Alzheimer's  
15 disease.

17. A method for inhibiting an ICE-mediated function in a patient comprising the step of administering to said patient a compound according to any  
20 one of claims 1-14 or a pharmaceutical composition according to claim 15.

18. A method for decreasing IGIF or IFN- $\gamma$  production in a patient comprising the step of  
25 administering to said patient a compound according to any one of claims 1-14 or a pharmaceutical composition according to claim 15.

19. The use of a compound according to any one of claims 1-14 or a pharmaceutical composition according to claim 15 in the manufacture of a medicament for treating or preventing a disease selected from an IL-1 mediated disease, an apoptosis mediated disease, an inflammatory disease, an autoimmune disease, a  
35 destructive bone disorder, a proliferative disorder, an

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infectious disease, a degenerative disease, a necrotic disease, an excess dietary alcohol intake disease, a viral mediated disease, inflammatory peritonitis, osteoarthritis, pancreatitis, asthma, adult respiratory distress syndrome, glomerulonephritis, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, chronic thyroiditis, Grave's disease, autoimmune gastritis, insulin-dependent diabetes mellitus (Type I), autoimmune hemolytic anemia, autoimmune neutropenia, 5 thrombocytopenia, chronic active hepatitis, myasthenia gravis, inflammatory bowel disease, Crohn's disease, psoriasis, graft vs host disease, osteoporosis, multiple myeloma-related bone disorder, acute myelogenous leukemia, chronic myelogenous leukemia, metastatic melanoma, Kaposi's sarcoma, multiple myeloma, sepsis, septic shock, Shigellosis, Alzheimer's disease, Parkinson's disease, cerebral ischemia, myocardial ischemia, spinal muscular atrophy, multiple sclerosis, AIDS-related encephalitis, HIV-related encephalitis, 10 aging, alopecia, neurological damage due to stroke, ulcerative colitis, traumatic brain injury, organ transplant rejection, hepatitis-B, hepatitis-C, hepatitis-G, yellow fever, dengue fever, or Japanese encephalitis, in a patient.

15

20

21. The use according to claim 20, wherein the disease is rheumatoid arthritis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, inflammatory peritonitis, septic shock, pancreatitis, traumatic brain injury, organ transplant rejection, osteoarthritis, asthma, psoriasis, or Alzheimer's disease.

30

22. The use of a compound according to any one 35 of claims 1-14 or a pharmaceutical composition according

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to claim 15 in the manufacture of a medicament for  
inhibiting an ICE-mediated function in a patient  
comprising the step of administering to said patient a  
compound according to any one of claims 1-14 or a  
5 pharmaceutical composition according to claim 15.

23. The use of a compound according to any one  
of claims 1-14 or a pharmaceutical composition according  
to claim 15 in the manufacture of a medicament for  
10 decreasing IGIF or IFN- $\gamma$  production in a patient  
comprising the step of administering to said patient a  
compound according to any one of claims 1-14 or a  
pharmaceutical composition according to claim 15.

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 99/05124

A. CLASSIFICATION OF SUBJECT MATTER	IPC 6 C07D243/02 A61K31/55	C07D401/14	C07D405/12	C07D401/12
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According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 552 400 A (ROLAND E. DOLLE ET AL.) 3 September 1996 cited in the application see column 3 - column 6 ----	1,19
A	US 5 716 929 A (GUY W. BEMIS ET AL.) 10 February 1998 see claims -----	1,19



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

\* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"Z" document member of the same patent family

Date of the actual completion of the international search

15 June 1999

Date of mailing of the international search report

29/06/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.  
Fax: (+31-70) 340-3016

Authorized officer

Van Bijlen, H

**INTERNATIONAL SEARCH REPORT**

International application No.

PCT/US 99/05124

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: 16-18

because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 16-18  
are directed to a method of treatment of the human/animal  
body, the search has been carried out and based on the alleged  
effects of the compound/composition.

2.  Claims Nos.:

because they relate to parts of the International Application that do not comply with the prescribed requirements to such  
an extent that no meaningful International Search can be carried out, specifically:

3.  Claims Nos.:

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all  
searchable claims.

2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment  
of any additional fee.

3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report  
covers only those claims for which fees were paid, specifically claims Nos.:

4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is  
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/05124

Patent document cited in search report	Publication date	Patent family member(s)			Publication date
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